

Appendix A. Detailed Electronic Database Search Strategies

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PubMed,

(immunotherapy[mesh] OR immunotherap*[tiab]) AND (asthma[mh] OR asthma[tiab]) NOT (“occupational diseases” [mh]) NOT (animals[mh] NOT humans[mh])

1. immunotherapy [mh]
2. immunotherap*[tiab]
3. 1 OR 2
4. asthma [mh]
5. asthma [tiab]
6. 4 OR 5
7. “occupational diseases” [mh]
8. 6 NOT 7
9. 3 AND 8
10. (animals[mh] NOT humans[mh])
11. 9 NOT 10
12. 11 AND (2005 to present [date-publication])

Embase

(‘immunotherapy’/exp OR immunotherapy) AND (‘asthma’/de OR asthma)

1. ‘immunotherapy’/exp OR immunotherapy
2. ‘asthma’/de OR asthma
3. 1 AND 2
4. 3 AND (2005 to present)

Cochrane Central Register of Controlled Trials (CENTRAL).

"immunotherapy" AND "asthma" in Title, Abstract, Keywords, Publication Year from 2005 to 2016 in Trials'

Appendix B. Glossary and List of Definitions

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Glossary

AIT	Allergen Immunotherapy
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
μg	microgram
BU	Biological units
SQU	Standard quality units
PNU	Protein Nitrogen Unit
AU	Allergy unit
Ag/ml	major protein unit; Antigen per ml
TU	Treatment units
wt/vol	Weight to volume
SE	Specific units of short-term immunotherapy
IR	Index of reactivity unit
ACT	Asthma Control Test
ACQ	Ashtma Control Questionnaire
P-ACT	Pediatric- Asthma Control Test
QOL	Quality of life
AQLQ	Asthma Quality of Life Questionnaire
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
PEF	Peak Expiratory Flow Rate
Ig	Immunoglobulin

List of Definitions

1. Objective Tests:

- a) Spirometry (FEV1;FVC;FEV1/FVC ratio)
- b) PEF [peak expiratory flow rate]: as opposed to formal spirometry (which is performed in a physician's office), the patient can use a home peak flow meter (hand-held device) to check his/her peak flow readings on a regular basis.
- c) Methacholine challenge: research tool in which a chemical irritant substance is inhaled into the airways in a controlled fashion to induce asthma symptoms. It can be used to diagnose asthma, characterize the severity of asthma, and/or assess the patient's response to treatment.

- d) Allergen challenge testing: research tool in which allergen is introduced into the airways in a controlled fashion to reproduce allergen-induced asthma symptoms and characterize the patient's allergic response and response to treatment.
- e) Exercise challenge: research tool in which intense exercise is used to trigger asthma symptoms, spirometry tests before and after to provide evidence of exercise-induced bronchoconstriction.

2. Medications:

- a) Long term control medications: Long term control medications are used daily to achieve and maintain control of persistent asthma. The most effective are those that attenuate the underlying inflammation characteristic of asthma. Long term control medications include corticosteroids, cromolyn sodium and nedocromyl, immunomodulators, leukotriene modifiers, long-acting bronchodilators and methylxanthines.
<https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf>
- b) Quick-relief medication: Quick-relief medications are used to treat acute symptoms and exacerbations. They include the following: short-acting beta agonists (SABA), anticholinergics and systemic corticosteroids.
<https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf>
- c) Systemic corticosteroids: There are potent anti-inflammatory medications, usually used in oral forms, for treatment of asthma. They can be used in the short term for quick relief or long term as long term control medications.
<https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf>
- d) Placebo: Any dummy medication or treatment. Although placebos originally were medicinal preparations having no specific pharmacological activity against a targeted condition, the concept has been extended to include treatments or procedures, especially those administered to control groups in clinical trials in order to provide baseline measurements for the experimental protocol. <https://www.drugs.com/article/placebo-effect.html>

Medications for asthma care

<https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report>

- a) Corticosteroids: anti-inflammatory medications that reduce airway hyperresponsiveness, inhibit inflammatory cell migration and activation, and block late phase reaction to allergen
 - i. Inhaled corticosteroid (ICS): beclomethasone dipropionate (QVAR, Vanceril, Beclovent), budesonide (Pulmicort), flunisolide (Aerobid), mometasone, fluticasone propionate (Flovent), triamcinolone acetonide (Azmacort)
 - ii. Systemic corticosteroids: Prednisone, Prednisolone (Prelone, Pediapred), Methylprednisolone (Medrol, Solu-Medrol), Triamcinolone (Kenalog).
- b) Leukotriene antagonist (LTRA): A class of drugs designed to prevent leukotriene synthesis or activity by blocking binding at the receptor level.
 Montelukast (Singulair), zafirlukast (Accolate), zileuton (Zyflo)
- c) Beta₂ agonists; Inhaled bronchodilators that relax smooth muscle.
 - i. Short acting beta agonists (SABAs) - duration of bronchodilation of less than 12 hours after a single dose; albuterol, levalbuterol, pirbuterol.
 - ii. Long acting beta agonist (LABAs) – duration of bronchodilation of at least 12 hours after a single dose; salmeterol and formoterol

- d) Cromolyn (Cromolyn sodium): A chromone complex that acts by inhibiting the release of chemical mediators from sensitized mast cells. It is used in the prophylactic treatment of both allergic and exercise-induced asthma, but does not affect an established asthmatic attack.
- e) Anticholinergics: Inhibit muscarinic cholinergic receptors and reduce vagal tone in the airway. Ipatropium is used as an alternative to SABAs or as added treatment.
- f) Methylxantines: bronchodilators that relax smooth muscle. Sustained-release theophylline is a mild to moderate bronchodilator used as adjunctive therapy.
- g) Immunomodulators: Omalizumab is an anti-IgE monoclonal antibody, therefore it prevents binding of IgE to its receptor in basophils and mast cells (prevents sensitization)

3. Efficacy measures

- a) Asthma symptoms: Recorded self-assessment of asthma signs and symptoms through validated scores. Validated scores included in this review are ACT, ACQ and P-ACT
<http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/act.php>
- b) Medication use: Need of daily medications. Reduction in long term control medication and quick relief medication.
- c) Quality of life (QOL): Asthma Quality of Life Questionnaire (AQLQ): There are 32 questions in the AQLQ addressing 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). The activity domain contains 5 ‘patient-specific’ questions. This allows patients to select 5 activities in which they are most limited and these activities will be assessed at each follow-up. Patients are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all - 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. (Includes strenuous activities (such as hurrying, exercising, running upstairs, sports), moderate activities (such as walking, housework, gardening, shopping, climbing stairs), social activities (such as talking, playing with pets/children, visiting friends/relatives), work-related activities, and sleeping.
<http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/aqlq.php>

4. Mechanistic Terms:

- a) Immunoglobulins (Ig): Multi-subunit proteins which function in immunity. They are produced by B lymphocytes from the immunoglobulins genes. They are comprised of two heavy chains (immunoglobulins heavy chains) and two light chains (immunoglobulins light chains) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms includes monomeric or polymeric forms, and transmembrane forms (B-Cell antigen receptors) or secreted forms (antibodies). They are divided by the amino acid sequence of their heavy chains into five classes; Immunoglobulin A (IgA), Immunoglobulin D (IgD), Immunoglobulins E (IgE), Immunoglobulin G (IgG), Immunoglobulin M (IgM), and various subclasses.
 - IgG: The major immunoglobulin isotype class in normal human serum. There are several isotype subclasses of IgG, for example, IgG1, IgG4, IgG2A, IgG2B.
 - IgE: An immunoglobulin associated with mast cells. Overexpression has been associated with allergic hypersensitivity.

- All other immunologic parameters, such as T-Lymphocytes (Lymphocytes responsible for cell-mediated immunity), cytokines (IL4/IL5/IL10/etc, non-antibody proteins that act as intercellular mediators) are not included as outcomes in this review.
- b) Sensitization: chain of cellular responses to induce an allergic response to a specific allergen. The allergen causes a chain of immunological responses; development of specific B and T cells, differentiation and clonal expansion of specific T-helpers and production of cytokines, with final induction of IgE production, and demonstrating a positive allergy skin test or positive specific IgE testing to that allergen.
http://www.nature.com/nri/journal/v6/n10/fig_tab/nri1934_F1.html
- Monosensitized: Patients who tested positive to only one allergen (or one family of related allergens) after being tested with a panel of allergens
 - Polysensitized: Patients who tested positive to multiple allergens after being tested with a panel of allergens

5. Safety terms

http://osp.od.nih.gov/sites/default/files/resources/Reporting_Guidelines.pdf

- a) Adverse events (AE): An injury caused by medical management—rather than by the underlying disease—which prolongs hospitalization, produces a disability, or both. Etiology: Drug effects, wound infections, technical complications, negligence, diagnostic mishaps, therapeutic mishaps, and events occurring in the emergency room.
- b) An adverse event is any undesirable experience associated with the use of a medical product in a patient. (Food and Drug Administration, 2009:
<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>)
- c) Serious adverse events (SAE): The event is serious and should be reported when the patient outcome is: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or requires intervention to prevent permanent impairment or damage. (Food and Drug Administration, 2009)
- d) When a particular condition causes the immune system to overreact, it is referred to as hypersensitivity reaction that triggers the production of IgE. These reactions may be damaging, uncomfortable, or occasionally fatal. <https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/hypersensitivity-reactions>
- e) Anaphylaxis: An acute hypersensitivity reaction (Type I IgE mediated allergic immediate reaction) due to exposure to a previously encountered antigen. The reaction may include rapidly progressing urticaria, respiratory distress, vascular collapse, systemic shock, and death.
http://www.worldallergy.org/professional/allergic_diseases_center/anaphylaxis/anaphylaxisSynopsis.php

Appendix C. List of Excluded Articles

Appendix C. List of Excluded Articles

Immunotherapy. CMAJ. 2005 Sep 13;173(6 Suppl):S46-50. PMID: 16157737.

No original data

Aasbjerg K, Dalhoff KP, Backer V. Adverse Events During Immunotherapy Against Grass Pollen-Induced Allergic Rhinitis - Differences Between Subcutaneous and Sublingual Treatment. Basic and Clinical Pharmacology and Toxicology. 2015;117(2):73-84.

No original data

Abbas AR, Jackman JK, Bullens SL, et al. Lung gene expression in a rhesus allergic asthma model correlates with physiologic parameters of disease and exhibits common and distinct pathways with human asthma and a mouse asthma model. Am J Pathol. 2011 Oct;179(4):1667-80. doi: 10.1016/j.ajpath.2011.06.009. PMID: 21819959.

Study is about efficacy but does not have a comparator group or is not an RCT; Does not apply to any Key Question

Acquistapace F, Agostinis F, Castella V, et al. Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case-control study on 171 patients. The EFESO-children multicenter trial. Pediatr Allergy Immunol. 2009 Nov;20(7):660-4. doi: 10.1111/j.1399-3038.2009.00860.x. PMID: 19320852.

Not allergic asthma

Adamic K, Zidarn M, Bajrovic N, et al. The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy. Wien Klin Wochenschr. 2009;121(9-10):357-60. doi: 10.1007/s00508-009-1172-0. PMID: 19562302.

Included multiple allergic conditions; outcomes not reported separately for asthma

Agache I, Ciobanu C. Risk factors and asthma phenotypes in children and adults with seasonal allergic rhinitis. Phys Sportsmed. 2010 Dec;38(4):81-6. doi: 10.3810/psm.2010.12.1829. PMID: 21150146.

Not allergic asthma; Does not apply to any Key Question

Agostinis F, Foglia C, Bruno ME, et al. Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen. Eur Ann Allergy Clin Immunol. 2009 Dec;41(6):177-80. PMID: 20128231.

Included multiple allergic conditions; outcomes not reported separately for asthma

Agostinis F, Tellarini L, Canonica GW, et al. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. Allergy. 2005 Jan;60(1):133. doi: 10.1111/j.1398-9952.2004.00616.x. PMID: 15575951.

Other: survey data on safety

Ajduk J, Marinic I, Aberle N, et al. Effect of house dust mite immunotherapy on transforming growth factor beta1-producing T cells in asthmatic children. Ann Allergy Asthma Immunol. 2008 Apr;100(4):314-22. doi: 10.1016/s1081-1206(10)60592-3. PMID: 18450115.

Study is about efficacy but does not have a comparator group or is not an RCT

Akmanlar N, Altintas DU, Guneser KS, et al. Comparison of conventional and rush immunotherapy with der PI in childhood respiratory allergy. Allergol Immunopathol (Madr). 2000 Jul-Aug;28(4):213-8. PMID: 11022267.

Included multiple allergic conditions; outcomes not reported separately for asthma

Aksoy F, Yildirim YS, Veyseller B, et al. Serum levels of advanced oxidation protein products in response to allergen exposure in allergic rhinitis. Ear Nose Throat J. 2012 Aug;91(8):E32-5. PMID: 22930093. Not allergic asthma

Alexander C, Tarzi M, Larche M, et al. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. Allergy. 2005 Oct;60(10):1269-74. doi: 10.1111/j.1398-9952.2005.00885.x. PMID: 16134993.

Does not include SCIT or SLIT

Alvarez-Cuesta E, Berges-Gimeno P, Gonzalez-Mancebo E, et al. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. Allergy. 2007 Jul;62(7):810-7. doi: 10.1111/j.1398-9952.2007.01365.x. PMID: 17573730.

Included multiple allergic conditions; outcomes not reported separately for asthma

Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, et al. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol. 1994 Mar;93(3):556-66. PMID: 8151058.

Included multiple allergic conditions; outcomes not reported separately for asthma

Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol.* 2006 Jan;117(1):169-75. doi: 10.1016/j.jaci.2005.10.010. PMID: 16387602.

Included multiple allergic conditions; outcomes not reported separately for asthma

Angelini F, Pacciani V, Corrente S, et al. Dendritic cells modification during sublingual immunotherapy in children with allergic symptoms to house dust mites. *World J Pediatr.* 2011 Feb;7(1):24-30. doi: 10.1007/s12519-011-0242-3. PMID: 21191773.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Anolik R, Schwartz AM, Sajjan S, et al. Patient initiation and persistence with allergen immunotherapy. *Ann Allergy Asthma Immunol.* 2014 Jul;113(1):101-7. doi: 10.1016/j.anai.2014.04.008. PMID: 24814759.

Included multiple allergic conditions; outcomes not reported separately for asthma

Antico A, Pagani M, Crema A. Priming-like effect and successful desensitization after anaphylactic shock by latex sublingual immunotherapy. *Eur Ann Allergy Clin Immunol.* 2007 Oct;39(8):259-61. PMID: 18237003.

Food allergy/aeroallergen NOT related to asthma; Other: latex SLIT

Antonova LP, Romanov VV, Averbakh MM, (2008). [Experience with bronchomunal used in the combined treatment of patients with bronchial asthma and chronic obstructive pulmonary disease]. Problemy tuberkuleza i boleznei legkikh, (4), #Pages#

Does not include SCIT or SLIT

Ariano R, Berto P, Incorvaia C, et al. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol.* 2009 Sep;103(3):254-9. doi: 10.1016/s1081-1206(10)60190-1. PMID: 19788024. **No outcomes of interest**

Ariano R, Incorvaia C, La Grutta S, et al. Safety of sublingual immunotherapy started during the pollen season. *Curr Med Res Opin.* 2009 Jan;25(1):103-7. doi: 10.1185/03007990802591673. PMID: 19210143.

Included multiple allergic conditions; outcomes not reported separately for asthma

Ariano R, Panzani RC, Mistrello G. Efficacy of sublingual coseasonal immunotherapy with a monomeric allergoid in Cupressaceae pollen allergy--preliminary data. *Eur Ann Allergy Clin Immunol.* 2005 Mar;37(3):103-8. PMID: 15918297.

Included multiple allergic conditions; outcomes not reported separately for asthma

Arvidsson MB, Lowhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. *Allergy.* 2004 Jan;59(1):74-80. PMID: 14674937.

Not allergic asthma

Aydogan M, Eifan AO, Keles S, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. *Respir Med.* 2013 Sep;107(9):1322-9. doi: 10.1016/j.rmed.2013.06.021. PMID: 23886432.

Not allergic asthma

Bag O, Can D, Karaarslan U, et al. The long-term outcomes of persistent childhood allergic asthma: a cross-sectional study from western Anatolia: childhood persistent asthma in western Anatolia. *Allergol Immunopathol (Madr).* 2013 Sep-Oct;41(5):315-9. doi: 10.1016/j.aller.2012.05.008. PMID: 23137869.

Does not include SCIT or SLIT

Bahcecici Erdem S, Nacaroglu HT, Karaman S, et al. Risk of systemic allergic reactions to allergen immunotherapy in a pediatric allergy clinic in Turkey. *Int J Pediatr Otorhinolaryngol.* 2016 May;84:55-60. doi: 10.1016/j.ijporl.2016.02.032. PMID: 27063754.

Included multiple allergic conditions; outcomes not reported separately for asthma

Bahceciler NN, Arikan C, Taylor A, et al. Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. *Int Arch Allergy Immunol.* 2005 Mar;136(3):287-94. doi: 10.1159/000083956. PMID: 15722639.

Study is about efficacy but does not have a comparator group or is not an RCT

Beitia JM, Lopez-Matas MA, Alonso A, et al. Allergenic profile to Phleum pratense and immunological changes induced after grass allergen-specific immunotherapy. *Int Arch Allergy Immunol.* 2014;165(1):9-17. doi: 10.1159/000365866. PMID: 25277364. **Included multiple allergic conditions; outcomes not reported separately for asthma**

Bernaola G, Corzo JL, Dominguez-Ortega J, et al. Sublingual immunotherapy: factors influencing adherence. *J Investig Allergol Clin Immunol*. 2012;22(6):458-9. PMID: 23101200.

Does not apply to any Key Question

Bernardini R, Campodonico P, Burastero S, et al. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. *Curr Med Res Opin*. 2006 Aug;22(8):1515-22. doi: 10.1185/030079906x115711. PMID: 16870076.

Not allergic asthma; Other: latex

Blume SW, Yeomans K, Allen-Ramey F, et al. Administration and Burden of Subcutaneous Immunotherapy for Allergic Rhinitis in U.S. and Canadian Clinical Practice. *J Manag Care Spec Pharm*. 2015 Nov;21(11):982-90. doi: 10.18553/jmcp.2015.21.11.982. PMID: 26521110.

Other: no safety data and not an RCT

Bouchaud G, Braza F, Chesne J, et al. Prevention of allergic asthma through Der p 2 peptide vaccination. *J Allergy Clin Immunol*. 2015 Jul;136(1):197-200 e1. doi: 10.1016/j.jaci.2014.12.1938. PMID: 25680456.

Animals or in vitro

Bozek A, Kolodziejczyk K, Bednarski P. The relationship between autoimmunity and specific immunotherapy for allergic diseases. *Hum Vaccin Immunother*. 2015;11(12):2764-8. doi:10.1080/21645515.2015.1087627. PMID: 26431066.

Included multiple allergic conditions; outcomes not reported separately for asthma

Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, et al. Pre-seasonal, subcutaneous immunotherapy: A double-blinded, placebo-controlled study in elderly patients with an allergy to grass. *Annals of Allergy, Asthma and Immunology*. 2016;116(2):156-61.

Not allergic asthma

Bozek A, Kolodziejczyk K, Warkocka-Szoltysek B, et al. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*. 2014 Sep-Oct;28(5):423-7. doi: 10.2500/ajra.2014.28.4091. PMID: 25198030.

Included multiple allergic conditions; outcomes not reported separately for asthma

Bozek A, Kozlowska R, Jarzab J. The safety of specific immunotherapy for patients allergic to house-dust mites and pollen in relation to the development of neoplasia and autoimmune disease: a long-term, observational case-control study. *Int Arch Allergy Immunol*. 2014;163(4):307-12. doi: 10.1159/000361022. PMID: 24776522.

Included multiple allergic conditions; outcomes not reported separately for asthma

Bush RK, Swenson C, Fahlberg B, et al. House dust mite sublingual immunotherapy: results of a US trial. *J Allergy Clin Immunol*. 2011 Apr;127(4):974-81 e1-7. doi: 10.1016/j.jaci.2010.11.045. PMID: 21333346.

Not allergic asthma

Bussmann C, Maintz L, Hart J, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin Exp Allergy*. 2007 Sep;37(9):1277-85. doi: 10.1111/j.1365-2222.2007.02783.x. PMID: 17845407.

Included multiple allergic conditions; outcomes not reported separately for asthma

Cadario G, Ciprandi G, Di Cara G, et al. Comparison between continuous or intermittent schedules of sublingual immunotherapy for house dust mites: effects on compliance, patients satisfaction, quality of life and safety. *Int J Immunopathol Pharmacol*. 2008 Apr-Jun;21(2):471-3. PMID: 18547495.

Not allergic asthma

Caimmi D, Barber D, Hoffmann-Sommergruber K, et al. Understanding the molecular sensitization for Cypress pollen and peach in the Languedoc-Roussillon area. *Allergy*. 2013 Feb;68(2):249-51. doi: 10.1111/all.12073. PMID: 23205629.

Does not include SCIT or SLIT

Calderon MA, Cox LS. Monoallergen sublingual immunotherapy versus multiallergen subcutaneous immunotherapy for allergic respiratory diseases: a debate during the AAAAI 2013 Annual Meeting in San Antonio, Texas. *J Allergy Clin Immunol Pract*. 2014 Mar-Apr;2(2):136-43. doi: 10.1016/j.jaip.2013.12.008. PMID: 24607039.

No original data

Calderon MA, Larenas D, Kleine-Tebbe J, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. *Allergy*. 2011 Oct;66(10):1345-59. doi: 10.1111/j.1365-9995.2011.02669.x. PMID: 21707645.

No original data

Calvani M, Sopo SM. Exercise-induced anaphylaxis caused by wheat during specific oral tolerance induction. *Ann Allergy Asthma Immunol*. 2007 Jan;98(1):98-9. doi: 10.1016/s1081-1206(10)60869-1. PMID: 17225729.

Does not apply to any Key Question; Does not include SCIT or SLIT

Caminati M, Dama AR, Djuric I, et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. *Expert Rev Clin Immunol.* 2015 Feb;11(2):233-45. doi: 10.1586/1744666x.2015.988143. PMID: 25484197.

No original data

Cantani A, Micera M. Significant decrease of IgE antibodies after a three-year controlled study of specific immunotherapy to pollen allergens in children with allergic asthma. *Eur Rev Med Pharmacol Sci.* 2005 Mar-Apr;9(2):103-11. PMID: 15945499.

Study is about efficacy but does not have a comparator group or is not an RCT

Cantani A, Micera M. A prospective study of asthma desensitization in 1182 children, 592 asthmatic children and 590 nonatopic controls. *Eur Rev Med Pharmacol Sci.* 2005 Nov-Dec;9(6):325-9. PMID: 16479736.

Included multiple allergic conditions; outcomes not reported separately for asthma

Carbone R, Luppi F, Monselise A, et al. Bronchial hyperresponsiveness in asthmatic adults--a long-term correlation study. *Eur Rev Med Pharmacol Sci.* 2005 Mar-Apr;9(2):125-31. PMID: 15945502.

Does not apply to any Key Question

Cardona R, Lopez E, Beltrán J, et al. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultra-rush buildup. A retrospective study. *Allergologia et Immunopathologia.* 2014;42(2):90-5.

Duplicate of another study

Casanovas M, Martin R, Jimenez C, et al. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Int Arch Allergy Immunol.* 2006;139(2):153-8. doi: 10.1159/000090392. PMID: 16374026.

Does not apply to any Key Question; Mixed population

Casanovas M, Martin R, Jimenez C, et al. Safety of immunotherapy with therapeutic vaccines containing depigmented and polymerized allergen extracts. *Clin Exp Allergy.* 2007 Mar;37(3):434-40. doi: 10.1111/j.1365-2222.2007.02667.x. PMID: 17359393.

Study is about efficacy but does not have a comparator group or is not an RCT; Included multiple allergic conditions; outcomes not reported separately for asthma

Chaker AM, Shamji MH, Dumitru FA, et al. Short-term subcutaneous grass pollen immunotherapy under the umbrella of anti-IL-4: A randomized controlled trial. *J Allergy Clin Immunol.* 2016 Feb;137(2):452-61 e9. doi: 10.1016/j.jaci.2015.08.046. PMID: 26531865.

Included multiple allergic conditions; outcomes not reported separately for asthma

Chen S, Wang L, Liao F, Zeng X, Xing QB, Chen B, Lin XZ, (2014). [Efficacy of sublingual immunotherapy with Dermatophagoides farinae drops in preschool and school-age children with allergic asthma and allergic rhinitis]. *Israel Medical Association Journal,* 16(#issue#), 539-543

Included multiple allergic conditions; outcomes not reported separately for asthma

Chen ZG, Li M, Chen YF, et al. Effects of dermatophagoides pteronyssinus allergen-specific immunotherapy on the serum interleukin-13 and pulmonary functions in asthmatic children. *Chin Med J (Engl).* 2009 May 20;122(10):1157-61. PMID: 19493463.

No data provided

Chen J, Li B, Zhao Y, et al. A prospective multicenter study of systemic reactions in standardized specific immunotherapy for allergic rhinitis in China. *Am J Rhinol Allergy.* 2014 Jan-Feb;28(1):e40-4. doi: 10.2500/ajra.2014.28.4005. PMID: 24717880.

Included multiple allergic conditions; outcomes not reported separately for asthma

Chen S, Zeng X, Wang L, Chen B, Chen L, Wu S, Liao F, Feng X, (2016). [Effects of house dust mite sublingual immunotherapy in children with allergic rhinitis and asthma]. *Annals of Allergy, Asthma and Immunology,* 116(#issue#), 194-198

Included multiple allergic conditions; outcomes not reported separately for asthma

Ciepiela O, Zawadzka-Krajewska A, Kotula I, et al. Influence of sublingual immunotherapy on the expression of Mac-1 integrin in neutrophils from asthmatic children. *Adv Exp Med Biol.* 2013;756:73-80. doi: 10.1007/978-94-007-4549-0_10. PMID: 22836621.

Does not apply to any Key Question

Ciepiela O, Zawadzka-Krajewska A, Kotula I, et al. Sublingual Immunotherapy for Asthma: Affects T-Cells but Does not Impact Basophil Activation. *Pediatr Allergy Immunol Pulmonol.* 2014 Mar 1;27(1):17-23. doi: 10.1089/ped.2014.0328. PMID: 24669352.

Other: basophil and t-cell activation only; Study is about efficacy but does not have a comparator group or is not an RCT

Ciepiela O, Zawadzka-Krajewska A, Kotula I, et al. The influence of sublingual immunotherapy on several parameters of immunological response in children suffering from atopic asthma and allergic rhinitis depending on asthma features. *Pneumonol Alergol Pol.* 2014;82(6):503-10. doi: 10.5603/PiAP.2014.0067. PMID: 25339560.

Study is about efficacy but does not have a comparator group or is not an RCT

Ciprandi G, Cadario G, Di Gioacchino M, et al. Sublingual immunotherapy in polysensitized allergic patients with rhinitis and/or asthma: allergist choices and treatment efficacy. *J Biol Regul Homeost Agents.* 2009 Jul-Sep;23(3):165-71. PMID: 19828093.

Study is about efficacy but does not have a comparator group or is not an RCT

Ciprandi G, De Amici M, Murdaca G, et al. Adipokines and sublingual immunotherapy: preliminary report. *Hum Immunol.* 2009 Jan;70(1):73-8. doi: 10.1016/j.humimm.2008.10.001. PMID: 19028536.

Not allergic asthma

Ciprandi G, Incorvaia C, Dell'Albani I, et al. Characteristics of candidates for allergen immunotherapy. *Allergy Rhinol (Providence).* 2013 Summer;4(2):e77-81. doi: 10.2500/ar.2013.4.0061. PMID: 24124641.

Not allergic asthma

Ciprandi G, Melioli G, Passalacqua G, et al. Immunotherapy in polysensitized patients: new chances for the allergists? *Ann Allergy Asthma Immunol.* 2012 Dec;109(6):392-4. doi: 10.1016/j.anai.2012.09.006. PMID: 23176875.

No original data

Cohon A, Arruda LK, Martins MA, et al. Evaluation of BCG administration as an adjuvant to specific immunotherapy in asthmatic children with mite allergy. *J Allergy Clin Immunol.* 2007 Jul;120(1):210-3. doi: 10.1016/j.jaci.2007.04.018. PMID: 17531299.

No original data; Study is about efficacy but does not have a comparator group or is not an RCT

Colas C, Monzon S, Venturini M, et al. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol.* 2006 Apr;117(4):810-6. doi: 10.1016/j.jaci.2005.11.039. PMID: 16630938.

Included multiple allergic conditions; outcomes not reported separately for asthma

Columbo M, Wong B, Panettieri RA, Jr., et al. The effect of multiple allergen immunotherapy on exhaled nitric oxide in adults with allergic rhinitis. *Allergy Asthma Clin Immunol.* 2013;9(1):31. doi: 10.1186/1710-1492-9-31. PMID: 23958488. **Not allergic asthma; Study is about efficacy but does not have a comparator group or is not an RCT**

Corrigan CJ, Kettner J, Doemer C, et al. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy.* 2005 Jun;60(6):801-7. doi: 10.1111/j.1398-9995.2005.00790.x. PMID: 15876311.

Included multiple allergic conditions; outcomes not reported separately for asthma

Cortellini G, Severino M, Francescato E, et al. Evaluation and validation of a bee venom sting challenge performed by a micro-syringe. *Ann Allergy Asthma Immunol.* 2012 Dec;109(6):438-41. doi: 10.1016/j.anai.2012.09.003. PMID: 23176884.

Does not apply to any Key Question

Cortellini G, Spadolini I, Patella V, et al. Sublingual immunotherapy for *Alternaria*-induced allergic rhinitis: a randomized placebo-controlled trial. *Ann Allergy Asthma Immunol.* 2010 Nov;105(5):382-6. doi: 10.1016/j.anai.2010.08.007. PMID: 21055665.

Included multiple allergic conditions; outcomes not reported separately for asthma

Cortellini G, Spadolini I, Santucci A, et al. Improvement of shrimp allergy after sublingual immunotherapy for house dust mites: a case report. *Eur Ann Allergy Clin Immunol.* 2011 Oct;43(5):162-4. PMID: 22145252.

Food allergy/aeroallergen NOT related to asthma; Study is about efficacy but does not have a comparator group or is not an RCT

Cosmi L, Santarlasci V, Angeli R, et al. Sublingual immunotherapy with *Dermatophagoides monomeric allergoid* down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. *Clin Exp Allergy.* 2006 Mar;36(3):261-72. doi: 10.1111/j.1365-2222.2006.02429.x. PMID: 16499636.

Included multiple allergic conditions; outcomes not reported separately for asthma

Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol.*

2014 Mar;133(3):751-8. doi:
10.1016/j.jaci.2013.10.041. PMID: 24332263.
Included multiple allergic conditions; outcomes not reported separately for asthma

Cruz NV, Bahna SL. Fever, urticaria, lymphadenopathy, and protracted arthralgia and myalgia resistant to corticosteroid therapy. *Allergy Asthma Proc.* 2011 Sep-Oct;32(5):395-8. doi: 10.2500/aap.2011.32.3437. PMID: 22195694.

Not allergic asthma

Czarnecka-Operacz M, Jenerowicz D, Silny W. Oral allergy syndrome in patients with airborne pollen allergy treated with specific immunotherapy. *Acta Dermatovenerol Croat.* 2008;16(1):19-24. PMID: 18358104.

Study is about efficacy but does not have a comparator group or is not an RCT

Dai L, Huang Y, Wang Y, Han HL, Li QB, Jiang YH, (2014). [Serious systemic adverse events associated with allergen-specific immunotherapy in children with asthma]. *International Archives of Allergy and Immunology*, 165(#issue#), 140-147

Other; Does not report outcomes of interest

D'Anneo RW, Bruno ME, Falagiani P. Sublingual allergoid immunotherapy: a new 4-day induction phase in patients allergic to house dust mites. *Int J Immunopathol Pharmacol.* 2010 Apr-Jun;23(2):553-60. PMID: 20646350.

Included multiple allergic conditions; outcomes not reported separately for asthma

de Blay F, Barnig C, Kanny G, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol.* 2007 Nov;99(5):453-61. PMID: 18051216.

Included multiple allergic conditions; outcomes not reported separately for asthma

de Bot CM, Moed H, Berger MY, et al. Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment. *BMC Fam Pract.* 2008;9:59. doi: 10.1186/1471-2296-9-59. PMID: 18937864.

Not allergic asthma; Does not apply to any Key Question

de Vos G, Shankar V, Nazari R, et al. Fear of repeated injections in children younger than 4 years receiving subcutaneous allergy immunotherapy. *Ann Allergy Asthma Immunol.* 2012 Dec;109(6):465-9. doi: 10.1016/j.anai.2012.10.003. PMID: 23176889.

Does not apply to any Key Question

Dehlink E, Eiwegger T, Gerstmayr M, et al. Absence of systemic immunologic changes during dose build-up phase and early maintenance period in effective specific sublingual immunotherapy in children. *Clin Exp Allergy.* 2006 Jan;36(1):32-9. doi: 10.1111/j.1365-2222.2006.02400.x. PMID: 16393263.

Included multiple allergic conditions; outcomes not reported separately for asthma

Demoly P, Broue-Chabbert A, Wessel F, et al. Severity and disease control before house dust mite immunotherapy initiation: ANTARES a French observational survey. *Allergy Asthma Clin Immunol.* 2016;12:13. doi: 10.1186/s13223-016-0119-z. PMID: 27069487.

Study is about efficacy but does not have a comparator group or is not an RCT

Di Renzo V, Cadario G, Grieco T, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, open, parallel-group study. *Ann Allergy Asthma Immunol.* 2014 Dec;113(6):671-3 e1. doi: 10.1016/j.anai.2014.09.009. PMID: 25304342.

Included multiple allergic conditions; outcomes not reported separately for asthma

Didier A, Bons B. Safety and tolerability of 5-grass pollen tablet sublingual immunotherapy: pooled analysis and clinical review. *Expert Opin Drug Saf.* 2015 May;14(5):777-88. doi: 10.1517/14740338.2015.1017468. PMID: 25732009.

No original data

Dinakar C, Van Osdol TJ, Barnes CS, et al. Changes in exhaled nitric oxide levels with immunotherapy. *Allergy Asthma Proc.* 2006 Mar-Apr;27(2):140-4. PMID: 16724633.

Does not apply to any Key Question; Mixed population

Ding LF, Chen Q, Li L, Liu JM, Zhang GP, Zhu XH, Wu AM, Ke JW, Dai YL, Wu CX, (2015). [Effects of sublingual immunotherapy on serum IL-17 and IL-35 levels in children with allergic rhinitis or asthma]. *Allergologia et Immunopathologia*, 43(#issue#), 25-31

Included multiple allergic conditions; outcomes not reported separately for asthma

Dokic D, Schnitker J, Narkus A, et al. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Prilozi.* 2005 Dec;26(2):113-29. PMID: 16400234.

Included multiple allergic conditions; outcomes not reported separately for asthma

Dominguez-Ortega J, Quirce S, Delgado J, et al. Diagnostic and therapeutic approaches in respiratory allergy are different depending on the profile of aeroallergen sensitisation. Allergol Immunopathol (Madr). 2014 Jan-Feb;42(1):11-8. doi: 10.1016/j.aller.2012.08.004. PMID: 23265263.

Does not include SCIT or SLIT

Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012 Mar;129(3):717-25 e5. doi: 10.1016/j.jaci.2011.12.973. PMID: 22285278.

Only Rhinoconjunctivitis outcomes

El-Qutob D, Moreno F, Subtil-Rodriguez A. Specific immunotherapy for rhinitis and asthma with a subcutaneous hypoallergenic high-dose house dust mite extract: results of a 9-month therapy. Immunotherapy. 2016 May 18doi: 10.2217/imt-2015-0017. PMID: 27188493.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Epstein TG, Liss GM, Murphy-Berendts K, et al. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? Ann Allergy Asthma Immunol. 2013 Apr;110(4):274-8, 8 e1. doi: 10.1016/j.anai.2013.01.015. PMID: 23535092.

Survey

Epstein TG, Liss GM, Murphy-Berendts K, et al. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). Ann Allergy Asthma Immunol. 2016 Apr;116(4):354-9 e2. doi: 10.1016/j.anai.2016.02.001. PMID: 26948485.

Survey

Etto T, de Boer C, Prickett S, et al. Unique and cross-reactive T cell epitope peptides of the major Bahia grass pollen allergen, Pas n 1. Int Arch Allergy Immunol. 2012;159(4):355-66. doi: 10.1159/000338290. PMID: 22832594.

Not allergic asthma

Farid R, Ghasemi R, Baradaran-Rahimi M, et al. Evaluation of six years allergen immunotherapy in allergic rhinitis and allergic asthma. Iran J Allergy Asthma Immunol. 2006 Mar;5(1):29-31. doi: 05.01/ijaa.2931. PMID: 17242501.

Included multiple allergic conditions; outcomes not reported separately for asthma

Feng H, Xiang L, Shen KL, (2010). [Dynamical changes of lung function and immunologic markers in asthmatic children receiving specific immunotherapy with standardized house dust mite extract]. Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics, 12(9), #Pages#

Study is about efficacy but does not have a comparator group or is not an RCT

Ferres J, Justicia JL, Garcia MP, et al. Efficacy of high-dose sublingual immunotherapy in children allergic to house dust mites in real-life clinical practice. Allergol Immunopathol (Madr). 2011 May-Jun;39(3):122-7. doi: 10.1016/j.aller.2010.01.008. PMID: 20570032.

Included multiple allergic conditions; outcomes not reported separately for asthma

Filanowicz M, Szynkiewicz E, Cegla B, et al. Analysis of the quality of life of patients with asthma and allergic rhinitis after immunotherapy. Postepy Dermatol Alergol. 2016 Apr;33(2):134-41. doi: 10.5114/pdia.2015.48061. PMID: 27279823.

Does not include SCIT or SLIT; Study is about efficacy but does not have a comparator group or is not an RCT

Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol. 2005 Sep;95(3):254-8. doi: 10.1016/s1081-1206(10)61222-7. PMID: 16200816.

Study is about efficacy but does not have a comparator group or is not an RCT

Frati F, Dell'Albani I, Incorvaia C. Long-term efficacy of allergen immunotherapy: what do we expect? Immunotherapy. 2013 Feb;5(2):131-3. doi: 10.2217/imt.12.154. PMID: 23413904

No original data

Frati F, Incorvaia C, Passalacqua G. Efficacy of sublingual immunotherapy. JAMA. 2013 Aug 14;310(6):643-4. doi: 10.1001/jama.2013.7646. PMID: 23942685.

No original data

Frew AJ, DuBuske L, Keith PK, et al. Assessment of specific immunotherapy efficacy using a novel placebo score-based method. Ann Allergy Asthma Immunol. 2012 Nov;109(5):342-7 e1. doi: 10.1016/j.anai.2012.08.013. PMID: 23062390.

No original data; Other: reanalysis of previously published clinical trial

Gammeri E, Arena A, D'Anneo R, et al. Safety and tolerability of ultra-Rush (20 minutes) sublingual immunotherapy in patients with allergic rhinitis

and/or asthma. Allergol Immunopathol (Madr). 2005 May-Jun;33(3):142-4. PMID: 15946626.

Included multiple allergic conditions; outcomes not reported separately for asthma

Gandarias B, Alonso MD, Fernandez Rivas M, et al. Retrospective study of tolerance to short initiation schedules in subcutaneous immunotherapy. J Investig Allergol Clin Immunol. 2005;15(4):242-8. PMID: 16433204.

Included multiple allergic conditions; outcomes not reported separately for asthma; Does not apply to any Key Question

Garcia Robaina JC, Polanco Sanchez C, Estella Perez E. Savings associated with high-dose hypoallergenic house dust mite immunotherapy in rhinitis and/or asthma patients in Spain. Clinicoecon Outcomes Res. 2016;8:235-41. doi: 10.2147/ceor.s107123. PMID: 27366098.

Included multiple allergic conditions; outcomes not reported separately for asthma

Garde J, Ferrer A, Jover V, et al. Tolerance of a Salsola kali extract standardized in biological units administered by subcutaneous route. Multicenter study. Allergol Immunopathol (Madr). 2005 Mar-Apr;33(2):100-4. PMID: 15808117.

Included multiple allergic conditions; outcomes not reported separately for asthma

Gentile DA. Sublingual immunotherapy improves symptoms of allergic rhinoconjunctivitis and asthma. Evid Based Med. 2014 Feb;19(1):34-5. doi: 10.1136/eb-2013-101371. PMID: 23935079.

No original data

Giordano T, Quarta C, Bruno ME, et al. Safety, tolerability and efficacy of sublingual allergoid immunotherapy with a 4-day shortened build-up phase. Eur Ann Allergy Clin Immunol. 2006 Nov;38(9):310-2. PMID: 17191751.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Greenberger PA. Terminology, close-calls, and bracketology for allergy, asthma, and immunology. Ann Allergy Asthma Immunol. 2013 Mar;110(3):141-5. doi: 10.1016/j.anai.2012.11.001. PMID: 23548520.

Does not apply to any Key Question; No original data

Grier TJ, Hall DM, Duncan EA, et al. Allergen stabilities and compatibilities in immunotherapy mixtures that contain cat, dog, dust mite, and cockroach extracts. Annals of Allergy, Asthma and Immunology. 2015;115(6):496-502.

Does not include SCIT or SLIT

Gulen F, Zeyrek D, Can D, et al. Development of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. Asian Pac J Allergy Immunol. 2007 Mar;25(1):7-11. PMID: 17891916.

Does not apply to any Key Question

Harding E. Sublingual dust mite immunotherapy for asthma. Lancet Respir Med. 2016 Jun;4(6):436. doi: 10.1016/s2213-2600(16)30101-1. PMID: 27174742.

No original data

Other: summary of an article in JAMA

Heale R. Short term coseasonal sublingual immunotherapy reduced the development of asthma in children with hay fever. Evid Based Nurs. 2005 Apr;8(2):44. PMID: 15830417.

No original data

Hedlin G, van Hage M. Severe asthma and allergy: mechanisms, diagnostics and treatment. J Intern Med. 2012 Aug;272(2):104-7. doi: 10.1111/j.1365-2796.2012.02557.x. PMID: 22632711.

No original data

Hernandez Fernandez de Rojas D, Antepara Ercoreca I, Ponte Tellechea A, et al. Phase I study of subcutaneous allergen immunotherapy with Dermatophagoides pteronyssinus in patients with allergic rhinoconjunctivitis with or without asthma. Immunotherapy. 2015;7(2):89-99. doi: 10.2217/imt.15.13. PMID: 25659029.

Included multiple allergic conditions; outcomes not reported separately for asthma

Hernandez N, Ibero M, Ridao M, et al. Safety of specific immunotherapy using a depigmented and polymerised extract of Dermatophagoides pteronyssinus in children under five years of age. Allergol Immunopathol (Madr). 2011 Sep-Oct;39(5):267-70. doi: 10.1016/j.aller.2010.09.002. PMID: 21334128.

Included multiple allergic conditions; outcomes not reported separately for asthma

Hiroi T, Kaminuma O, Takaiwa F. Vaccination with transgenic rice seed expressing mite allergen: a new option for asthma sufferers? Expert Rev Vaccines. 2011 Sep;10(9):1249-51. doi: 10.1586/erv.11.102. PMID: 21919612.

Animals or in vitro; No original data

Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol. 1997 Feb;8(1):21-7. PMID: 9260215.

Included multiple allergic conditions; outcomes not reported separately for asthma

Holt PG. Primary prevention by early intervention with specific immunotherapy. Drugs Today (Barc). 2008 Dec;44 Suppl B:75-7. PMID: 19221625.

No original data

Horst M, Hejjaoui A, Horst V, et al. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol. 1990 Feb;85(2):460-72. PMID: 2406323.

Included multiple allergic conditions; outcomes not reported separately for asthma

Hur GY, Kim TB, Han MY, et al. A survey of the prescription patterns of allergen immunotherapy in Korea. Allergy Asthma Immunol Res. 2013 Sep;5(5):277-82. doi: 10.4168/aaair.2013.5.5.277. PMID: 24003383.

Does not apply to any Key Question; Other: survey of physicians - mentions safety but nothing specific to patients

Ibero M, Justicia JL, Alvaro M, et al. Diagnosis and treatment of allergic rhinitis in children: results of the PETRA study. Allergol Immunopathol (Madr). 2012 May-Jun;40(3):138-43. doi: 10.1016/j.aller.2010.12.010. PMID: 21497009.

Included multiple allergic conditions; outcomes not reported separately for asthma

Inal A, Altintas DU, Yilmaz M, et al. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol. 2007;17(2):85-91. PMID: 17460946.

Included multiple allergic conditions; outcomes not reported separately for asthma

Inci D, Altintas DU, Kendirli SG, et al. The effect of specific immunotherapy on exhaled breath condensate nitrite levels. Allergy. 2006 Jul;61(7):899-900. doi: 10.1111/j.1398-9995.2006.01118.x. PMID: 16792595.

Does not apply to any Key Question; Mixed population

Ippoliti F, De Santis W, Volterrani A, et al. Psychological stress affects response to sublingual immunotherapy in asthmatic children allergic to house dust mite. Pediatr Allergy Immunol. 2006 Aug;17(5):337-45. doi: 10.1111/j.1399-3038.2006.00417.x. PMID: 16846451.

Does not apply to any Key Question; Other: comparator - different level of stress group

Irani C, Saleh RA, Jammal M, et al. High-dose sublingual immunotherapy in patients with

uncontrolled allergic rhinitis sensitized to pollen: a real-life clinical study. Int Forum Allergy Rhinol. 2014 Oct;4(10):802-7. doi: 10.1002/alr.21375. PMID: 25224283.

Included multiple allergic conditions; outcomes not reported separately for asthma

Ishida W, Fukuda K, Harada Y, et al. Oral immunotherapy for allergic conjunctivitis. Cornea. 2014 Nov;33 Suppl 11:S32-6. doi: 10.1097/ico.0000000000000241. PMID: 25289722.

No original data

Jacobsen L. Prevention of asthma and allergies. Drugs Today (Barc). 2008 Dec;44 Suppl B:79-82. PMID: 19221626

No original data

Janciauskiene S, Olejnicka B, Koczulla R, et al. Allergen-specific immunotherapy increases plasma gelsolin levels. Am J Rhinol Allergy. 2014 May-Jun;28(3):e136-40. doi: 10.2500/ajra.2014.28.4038. PMID: 24980225.

Other: no clinical data or Igs; Study is about efficacy but does not have a comparator group or is not an RCT

Jerzynska J, Stelmach W, Rychlik B, et al. The clinical effect of vitamin D supplementation combined with grass-specific sublingual immunotherapy in children with allergic rhinitis. Allergy Asthma Proc. 2016 Mar;37(2):105-14. doi: 10.2500/aap.2016.37.3921. PMID: 26932169.

Included multiple allergic conditions; outcomes not reported separately for asthma

Jourdy DN, Reisacher WR. Factors affecting time required to reach maintenance dose during subcutaneous immunotherapy. Int Forum Allergy Rhinol. 2012 Jul-Aug;2(4):294-9. doi: 10.1002/alr.21027. PMID: 22434700.

Does not apply to any Key Question

Jung K. Safety and tolerability of immunotherapy using various updosing schedules of a new SCIT product with an optimised allergen/aluminium hydroxide ratio. Allergy. 2011 Jul;66 Suppl 95:41-3. doi: 10.1111/j.1398-9995.2011.02632.x. PMID: 21668852.

Included multiple allergic conditions; outcomes not reported separately for asthma

Jutel M, Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol. 2005 Sep;116(3):608-13. doi: 10.1016/j.jaci.2005.06.004. PMID: 16159631.

Included multiple allergic conditions; outcomes not reported separately for asthma

Kamin W, Kopp MV, Erdnues F, et al. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol.* 2010 Feb;21(1 Pt 2):e160-5. doi: 10.1111/j.1399-3038.2009.00900.x. PMID: 19732370.

Included multiple allergic conditions; outcomes not reported separately for asthma; Not allergic asthma

Karaman S, Can D, Erdem SB, et al. Is There Any Parameter Helpful for Predicting a Suitable Candidate for Mite Immunotherapy? *Iran J Allergy Asthma Immunol.* 2016 Apr;15(2):105-11. PMID: 27090363.

Study is about efficacy but does not have a comparator group or is not an RCT; Other: study does not have safety data and is not an RCT

Keskin O, Tuncer A, Adalioglu G, et al. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. *Pediatr Allergy Immunol.* 2006 Sep;17(6):396-407. doi: 10.1111/j.1399-3038.2006.00442.x. PMID: 16925684.

Not allergic asthma

Kim H, Waserman S, Hebert J, et al. Efficacy and safety of ragweed sublingual immunotherapy in Canadian patients with allergic rhinoconjunctivitis. *Allergy Asthma Clin Immunol.* 2014;10(1):55. doi: 10.1186/1710-1492-10-55. PMID: 25788949.

Not allergic asthma; Included multiple allergic conditions; outcomes not reported separately for asthma

Klimek L, Bachert C, Lukat KF, et al. Allergy immunotherapy with a hypoallergenic recombinant birch pollen allergen rBet v 1-FV in a randomized controlled trial. *Clin Transl Allergy.* 2015;5:28. doi: 10.1186/s13601-015-0071-x. PMID: 26328056.

Included multiple allergic conditions; outcomes not reported separately for asthma

Klimek L, Schendzielorz P, Pinol R, et al. Specific subcutaneous immunotherapy with recombinant grass pollen allergens: first randomized dose-ranging safety study. *Clin Exp Allergy.* 2012 Jun;42(6):936-45. doi: 10.1111/j.1365-2222.2012.03971.x. PMID: 22909165.

Included multiple allergic conditions; outcomes not reported separately for asthma

Koberlein J, Kothe AC, Sieber J, et al. Determining factors of patient compliance to treatment in allergic rhinitis. *Asian Pac J Allergy Immunol.* 2013

Jun;31(2):148-56. doi: 10.12932/ap0264.31.2.2013. PMID: 23859415.

Not allergic asthma; No original data

Kofler H, Kurz K, Grander G, et al. Specific immunotherapy normalizes tryptophan concentrations in patients with allergic rhinitis. *Int Arch Allergy Immunol.* 2012;159(4):416-21. doi: 10.1159/000338937. PMID: 22846847.

Not allergic asthma

Kopp MV, Hamelmann E, Bendiks M, et al. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. *Pediatr Allergy Immunol.* 2013 Aug;24(5):427-33. doi: 10.1111/pai.12098. PMID: 23799935.

Other: omalizumab vs. SIT; Included multiple allergic conditions; outcomes not reported separately for asthma

Kopp MV, Hamelmann E, Zielen S, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy.* 2009 Feb;39(2):271-9. doi: 10.1111/j.1365-2222.2008.03121.x. PMID: 19016798.

Included multiple allergic conditions; outcomes not reported separately for asthma; Other: combo omalizumab + SIT

Kositz C, Schroecksnadel K, Grander G, et al. High serum tryptophan concentration in pollinosis patients is associated with unresponsiveness to pollen extract therapy. *Int Arch Allergy Immunol.* 2008;147(1):35-40. doi: 10.1159/000128584. PMID: 18446051.

Does not apply to any Key Question; Not allergic asthma

Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. *J Allergy Clin Immunol.* 2011 Feb;127(2):502-8 e1-6. doi: 10.1016/j.jaci.2010.11.036. PMID: 21281874.

Included multiple allergic conditions; outcomes not reported separately for asthma

Kuna P, Samolinski B, Worm M, et al. Sustained clinical efficacy of sublingual immunotherapy with a high-dose grass pollen extract. *Eur Ann Allergy Clin Immunol.* 2011 Aug;43(4):117-21. PMID: 21980799.

Included multiple allergic conditions; outcomes not reported separately for asthma

Kwong KY, Leibel S. Update on allergen immunotherapy for treatment of allergic diseases. *Adv Pediatr.* 2013;60(1):141-65. doi: 10.1016/j.yapd.2013.04.008. PMID: 24007843.

Study is about efficacy but does not have a comparator group or is not an RCT; No original data

La Rosa M, Lionetti E, Leonardi S, et al. Specific immunotherapy in children: the evidence. *Int J Immunopathol Pharmacol.* 2011 Oct;24(4 Suppl):69-78. PMID: 22032790.

No original data

Lambert N, Guiddir T, Amat F, et al. Pre-treatment by omalizumab allows allergen immunotherapy in children and young adults with severe allergic asthma. *Pediatr Allergy Immunol.* 2014 Dec;25(8):829-32. doi: 10.1111/pai.12306. PMID: 25387446.

Study is about efficacy but does not have a comparator group or is not an RCT

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No original data; Does not apply to any Key Question

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Other; Not outcomes of interest

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Other: followup of eligible trial CAS; Does not apply to anyKey Question

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Does not apply to any Key Question

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Does not apply to any Key Question

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Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

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No original data; Does not include SCIT or SLIT

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Not allergic asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Does not apply to any Key Question; Mixed population

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No original data

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No original data; Mixed population

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Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

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No original data

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Animals or in vitro; Does not apply to any Key Question

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Not allergic asthma

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No original data; Does not apply to any Key Question

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Does not apply to any Key Question; Included multiple allergic conditions; outcomes not reported separately for asthma

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No original data

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Study is about efficacy but does not have a comparator group or is not an RCT; Does not apply to any Key Question

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No original data

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Not allergic asthma; Study is about efficacy but does not have a comparator group or is not an RCT

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Study is about efficacy but does not have a comparator group or is not an RCT

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Does not include SCIT or SLIT

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No original data

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Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

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Not allergic asthma; Included multiple allergic conditions; outcomes not reported separately for asthma

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Study is about efficacy but does not have a comparator group or is not an RCT; Included multiple allergic conditions; outcomes not reported separately for asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Am J Rhinol Allergy. 2010 May-Jun;24(3):220-5. doi: 10.2500/ajra.2010.24.3437. PMID: 20167138.

Included multiple allergic conditions; outcomes not reported separately for asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

Pfaar O, Sager A, Robinson DS. Safety and effect on reported symptoms of depigmented polymerized allergen immunotherapy: a retrospective study of 2927 paediatric patients. Pediatr Allergy Immunol. 2015 May;26(3):280-6. doi: 10.1111/pai.12347. PMID: 25640879.

Included multiple allergic conditions; outcomes not reported separately for asthma

Polanco C. Clinical And Economic Benefits Associated With Less Use Of Fluticasone In Pediatric Patients With Persistent Asthma Treated With High Doses Of Specific Allergen Immunotherapy To Mites. Value Health. 2015 Nov;18(7):A498. doi: 10.1016/j.jval.2015.09.1401. PMID: 26532795.

Abstract

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Does not apply to any Key Question

Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to Alternaria alternata: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. Curr Med Res Opin. 2010 Dec;26(12):2801-6. doi: 10.1185/03007995.2010.532201. PMID: 21050060.

Included multiple allergic conditions; outcomes not reported separately for asthma

Prieto L, Palacios R, Aldana D, et al. Effect of allergen-specific immunotherapy with purified Alt a1 on AMP responsiveness, exhaled nitric oxide and exhaled breath condensate pH: a randomized double blind study. Allergy Asthma Clin Immunol. 2010;6(1):27. doi: 10.1186/1710-1492-6-27. PMID: 20846390.

Included multiple allergic conditions; outcomes not reported separately for asthma

Purello-D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract

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Included multiple allergic conditions; outcomes not reported separately for asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

Quirce S. Asthma in Alergologica-2005. J Investigig Allergol Clin Immunol. 2009;19 Suppl 2:14-20. PMID: 19530413.

Does not apply to any Key Question

Rak S, Heinrich C, Jacobsen L, et al. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. J Allergy Clin Immunol. 2001 Dec;108(6):921-8. doi: 10.1067/mai.2001.119743. PMID: 11742269.

Not allergic asthma

Rak S. Quality of life (QoL): impact of specific immunotherapy (SIT) on social and physical ability. Drugs Today (Barc). 2008 Dec;44 Suppl B:35-8. PMID: 19221616.

No original data

Ras L, de Groot H, Stengs CH, et al. Persistence of treatment with 5-grass pollen tablets in patients with allergic rhinitis: a real-life study. Ann Allergy Asthma Immunol. 2016 Jan;116(1):52-8 e2. doi: 10.1016/j.anai.2015.10.018. PMID: 26596408.

Included multiple allergic conditions; outcomes not reported separately for asthma

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No original data

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Does not include SCIT or SLIT

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sublingual immunotherapy. Allergol Immunopathol (Madr). 2015 Jan-Feb;43(1):108-11. doi: 10.1016/j.aller.2013.09.007. PMID: 24388811.

Does not apply to any Key Question; Mixed population

Reich K, Gessner C, Kroker A, et al. Immunologic effects and tolerability profile of in-season initiation of a standardized-quality grass allergy immunotherapy tablet: a phase III, multicenter, randomized, double-blind, placebo-controlled trial in adults with grass pollen-induced rhinoconjunctivitis. Clin Ther. 2011 Jul;33(7):828-40. doi: 10.1016/j.clinthera.2011.06.006. PMID: 21741092.

Not allergic asthma

Reinhold T, Ostermann J, Thum-Oltmer S, et al. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. Clin Transl Allergy. 2013;3(1):30. doi: 10.1186/2045-7022-3-30. PMID: 24004637.

Does not apply to any Key Question

Rienzo VD, Minelli M, Musarra A, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy. 2005 May;35(5):560-4. doi: 10.1111/j.1365-2222.2005.02219.x. PMID: 15898975.

Included multiple allergic conditions; outcomes not reported separately for asthma; Survey

Rodriguez F, Boquete M, Ibanez MD, et al. Once daily sublingual immunotherapy without updosing--A new treatment schedule. Int Arch Allergy Immunol. 2006;140(4):321-6. doi: 10.1159/000093710. PMID: 16741368.

Included multiple allergic conditions; outcomes not reported separately for asthma

Rodriguez-Perez N, Ambriz-Moreno Mde J, Canonica GW, et al. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. Ann Allergy Asthma Immunol. 2008 Sep;101(3):304-10. PMID: 18814454.

Included multiple allergic conditions; outcomes not reported separately for asthma

Rogala B, Gluck J. Risks and benefits of allergen immunotherapy. Expert Opin Drug Saf. 2009 May;8(3):253-6. doi: 10.1517/14740330802457208. PMID: 19432555.

No original data

Roger A, Depreux N, Jurgens Y, et al. A novel and well tolerated mite allergoid subcutaneous immunotherapy: evidence of clinical and immunologic efficacy. Immun Inflamm Dis. 2014

Aug;2(2):92-8. doi: 10.1002/iid3.23. PMID: 25400929.

Mixed population

Roger A, Quilez E, Depreux N, et al. DIRAE study: seasonal allergic rhinitis distribution in Spain. Allergol Immunopathol (Madr). 2013 May-Jun;41(3):151-7. doi: 10.1016/j.aller.2012.03.005. PMID: 23141749.

Does not apply to any Key Question; Does not include SCIT or SLIT

Rosewich M, Girod K, Zielen S, et al. Induction of Bronchial Tolerance After 1 Cycle of Monophosphoryl-A-Adjuvanted Specific Immunotherapy in Children With Grass Pollen Allergies. Allergy Asthma Immunol Res. 2016 May;8(3):257-63. doi: 10.4168/aair.2016.8.3.257. PMID: 26922936.

Study is about efficacy but does not have a comparator group or is not an RCT

Rosewich M, Lee D, Zielen S. Pollinex Quattro: an innovative four injections immunotherapy in allergic rhinitis. Hum Vaccin Immunother. 2013 Jul;9(7):1523-31. doi: 10.4161/hv.24631. PMID: 23584250.

No original data

Rossi RE, Monasterolo G, Coco G, et al. Possible relationship between systemic side effects and sensitization to rPar j 2 in allergic patients submitted to an ultra-rush (20 min) sublingual immunotherapy and selected by component resolved diagnosis. Int Arch Allergy Immunol. 2005 Oct;138(2):105-10. doi: 10.1159/000088431. PMID: 16174987.

Included multiple allergic conditions; outcomes not reported separately for asthma

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Included multiple allergic conditions; outcomes not reported separately for asthma

Rottem M, Egbaria A. Subcutaneous immunotherapy in Northern Israel: efficacy and safety. Isr Med Assoc J. 2014 Sep;16(9):539-43. PMID: 25351009.

Included multiple allergic conditions; outcomes not reported separately for asthma

Sahadevan A, Cusack R, Lane SJ. Safety of Grass Pollen Sublingual Immunotherapy for Allergic Rhinitis in Concomitant Asthma. Ir Med J. 2015 Nov-Dec;108(10):304-7. PMID: 26817287.

Study is about efficacy but does not have a comparator group or is not an RCT

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No original data

Sambugaro R, Puccinelli P, Burastero SE, et al. The efficacy of sublingual immunotherapy for respiratory allergy is not affected by different dosage regimens in the induction phase. *Allergol Immunopathol (Madr)*. 2003 Nov-Dec;31(6):329-37. PMID: 14670288.

Not allergic asthma

Sastre J, Landivar ME, Ruiz-Garcia M, et al. How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area. *Allergy*. 2012 May;67(5):709-11. doi: 10.1111/j.1398-9995.2012.02808.x. PMID: 22379958.

Does not include SCIT or SLIT

Sastre J, Rodriguez F, Campo P, et al. Adverse reactions to immunotherapy are associated with different patterns of sensitization to grass allergens. *Allergy*. 2015 May;70(5):598-600. doi: 10.1111/all.12575. PMID: 25631061.

Included multiple allergic conditions; outcomes not reported separately for asthma

Sastre J, Vallejo L, Hernandez E, et al. Rush allergen subcutaneous immunotherapy administered with infusion pump. *Ann Allergy Asthma Immunol*. 2011 Nov;107(5):459-60. doi: 10.1016/j.anai.2010.12.003. PMID: 22018619.

Included multiple allergic conditions; outcomes not reported separately for asthma

Scadding GK. Further marches: allergic and non-allergic. *Clin Exp Allergy*. 2007 Apr;37(4):485-7. doi: 10.1111/j.1365-2222.2007.02675.x. PMID: 17430343.

No original data

Schmitt J, Stadler E, Kuster D, et al. Medical care and treatment of allergic rhinitis: a population-based cohort study based on routine healthcare utilization data. *Allergy*. 2016 Jun;71(6):850-8. doi: 10.1111/all.12838. PMID: 26749452.

Not allergic asthma; Other: cohort study with no safety data

Seidenberg J, Pajno GB, Bauer CP, et al. Safety and tolerability of seasonal ultra-rush, high-dose sublingual-swallow immunotherapy in allergic rhinitis to grass and tree pollens: an observational

study in 193 children and adolescents. *J Investig Allergol Clin Immunol*. 2009;19(2):125-31. PMID: 19476016.

Included multiple allergic conditions; outcomes not reported separately for asthma

Senti G, Johansen P, Haug S, et al. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/IIa clinical trial. *Clin Exp Allergy*. 2009 Apr;39(4):562-70. doi: 10.1111/j.1365-2222.2008.03191.x. PMID: 19226280.

Study is about efficacy but does not have a comparator group or is not an RCT; Other: includes an additive to SCIT

Serrano P, Justicia JL, Sanchez C, et al. Systemic tolerability of specific subcutaneous immunotherapy with index-of-reactivity-standardized allergen extracts administered using clustered regimens: a retrospective, observational, multicenter study. *Ann Allergy Asthma Immunol*. 2009 Mar;102(3):247-52. doi: 10.1016/s1081-1206(10)60088-9. PMID: 19354072.

Included multiple allergic conditions; outcomes not reported separately for asthma

Shaikh WA, Shaikh SW. Allergies in India: a study on medication compliance. *J Indian Med Assoc*. 2009 Jul;107(7):462-3. PMID: 20112853.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Sieber J, De Geest S, Shah-Hosseini K, et al. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. *Curr Med Res Opin*. 2011 Apr;27(4):855-61. doi: 10.1185/03007995.2011.559538. PMID: 21323505.

Not allergic asthma; Does not apply to any Key Question

Sieber J, Gross A, Shah-Hosseini K, et al. The RHINASTHMA GAV scores without SLIT, at the beginning and at the end of seasonal SLIT. *Asian Pac J Allergy Immunol*. 2010 Dec;28(4):232-6. PMID: 21337905.

Included multiple allergic conditions; outcomes not reported separately for asthma

Siemund I, Hindsen M, Netterlid E, et al. Contact allergy in atopic individuals in relation to allergen-specific immunotherapy. *Eur J Dermatol*. 2016 Jun 1;26(3):271-80. doi: 10.1684/ejd.2016.2765. PMID: 27193374.

Included multiple allergic conditions; outcomes not reported separately for asthma; Other: study

looks at atopic contact dermatitis as outcome, no asthma outcomes

Sikora JM, Tankersley MS. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. Ann Allergy Asthma Immunol. 2013 Mar;110(3):194-7 e4. doi: 10.1016/j.anai.2012.12.014. PMID: 23548531.

Does not apply to any Key Question

Sola J, da Silva Ferreira JA, Dionicio Elera J, et al. Timothy grass pollen therapeutic vaccine: optimal dose for subcutaneous immunotherapy. Immunotherapy. 2016;8(3):251-63. doi: 10.2217/imt.15.125. PMID: 26760111.

Not allergic asthma; Included multiple allergic conditions; outcomes not reported separately for asthma

Song W, Xie H, Chai R, Lin X, Song L, (2016). [Effect evaluation of allergen specific immunotherapy in patients with allergic rhinitis and asthma]. Annals of Allergy, Asthma and Immunology, 116(#issue#), 52-58.e2

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Soyyigit S, Guloglu D, Ikinciogullari A, et al. Immunologic alterations and efficacy of subcutaneous immunotherapy with Dermatophagoides pteronyssinus in monosensitized and polysensitized patients. Ann Allergy Asthma Immunol. 2016 Mar;116(3):244-51 e2. doi: 10.1016/j.anai.2016.01.002. PMID: 26945497.

Included multiple allergic conditions; outcomes not reported separately for asthma

Srivastava D, Singh BP, Arora N, et al. Clinico-immunologic study on immunotherapy with mixed and single insect allergens. J Clin Immunol. 2009 Sep;29(5):665-73. doi: 10.1007/s10875-009-9307-7. PMID: 19533313.

Included multiple allergic conditions; outcomes not reported separately for asthma

Srivastava D, Singh BP, Sudha VT, et al. Immunotherapy with mosquito (*Culex quinquefasciatus*) extract: a double-blind, placebo-controlled study. Ann Allergy Asthma Immunol. 2007 Sep;99(3):273-80. doi: 10.1016/s1081-1206(10)60664-3. PMID: 17910332.

Does not apply to any Key Question

Stelmach I, Kaluzinska-Parzyszek I, Jerzynska J, et al. Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. Allergy. 2012 Mar;67(3):312-20. doi:

10.1111/j.1398-9995.2011.02758.x. PMID: 22142341.

Mixed population

Stelmach I, Sobocinska A, Majak P, et al. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. Ann Allergy Asthma Immunol. 2012 Oct;109(4):274-8. doi: 10.1016/j.anai.2012.07.015. PMID: 23010234.

Not an RCT and has no safety data

Stelmaszczyk-Emmel A, Zawadzka-Krajewska A, Glodkowska-Mrowka E, et al. FoxP3 Tregs Response to Sublingual Allergen Specific Immunotherapy in Children Depends on the Manifestation of Allergy. J Immunol Res. 2015;2015:731381. doi: 10.1155/2015/731381. PMID: 26457309.

Included multiple allergic conditions; outcomes not reported separately for asthma; Other: immunology study, but IgG, IgE and skin testing not reported

Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. J Allergy Clin Immunol. 2005 Jul;116(1):109-18. doi: 10.1016/j.jaci.2005.05.005. PMID: 15990782.

Included multiple allergic conditions; outcomes not reported separately for asthma

Tabar AI, Gonzalez Delgado P, Sanchez Hernandez C, et al. Phase II/III clinical trial to assess the tolerability and immunological effect of a new updosing phase of Dermatophagoides mix-based immunotherapy. J Investig Allergol Clin Immunol. 2015;25(1):40-6. PMID: 25898693.

Included multiple allergic conditions; outcomes not reported separately for asthma

Tanaka Y, Okafuji I, Narabayashi S, et al. Safety and efficacy of one-year rush subcutaneous immunotherapy in Japanese children, using house dust extract. Japanese Journal of Allergology. 2015;64(8):1160-8.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr). 1990 Sep-Oct;18(5):277-84. PMID: 2097894.

Included multiple allergic conditions; outcomes not reported separately for asthma

Theodoropoulos DS, Stockdale CK, Duquette DR, et al. Inhalant allergy compounding the chronic

vaginitis syndrome: characterization of sensitization patterns, comorbidities and responses to sublingual immunotherapy. Arch Gynecol Obstet. 2016 Apr 4doi: 10.1007/s00404-016-4081-2. PMID: 27040422.

Not allergic asthma

Tian M, Wang Y, Lu Y, et al. Effects of sublingual immunotherapy for *Dermatophagoïdes farinae* on Th17 cells and CD4(+) CD25(+) regulatory T cells in peripheral blood of children with allergic asthma. Int Forum Allergy Rhinol. 2014 May;4(5):371-5. doi: 10.1002/ialr.21305. PMID: 24591191.

No outcomes of interest

Torres-Rodriguez JM, Pulido-Marrero Z, Vera-Garcia Y. Respiratory allergy to fungi in Barcelona, Spain: clinical aspects, diagnosis and specific treatment in a general allergy unit. Allergol Immunopathol (Madr). 2012 Sep-Oct;40(5):295-300. doi: 10.1016/j.aller.2011.09.003. PMID: 22136809.

Does not apply to any Key Question

Tosca M, Silvestri M, Accogli A, et al. Serum-specific IgE and allergen immunotherapy in allergic children. Immunotherapy. 2014;6(1):29-33. doi: 10.2217/imt.13.145. PMID: 24341881.

Study is about efficacy but does not have a comparator group or is not an RCT; Mixed population

Townley RG. Is sublingual immunotherapy "ready for prime time"? Chest. 2008 Mar;133(3):589-90. doi: 10.1378/chest.07-2620. PMID: 18321896.

No original data

Trebuchon F, Lheritier-Barrand M, David M, et al. Characteristics and management of sublingual allergen immunotherapy in children with allergic rhinitis and asthma induced by house dust mite allergens. Clin Transl Allergy. 2014;4:15. doi: 10.1186/2045-7022-4-15. PMID: 24910771.

Other: sub-analysis of previous study

Tripondi S, Di Renzo Businco A, Benincori N, et al. Safety and tolerability of ultra-rush induction, less than one hour, of sublingual immunotherapy in children. Int Arch Allergy Immunol. 2006;139(2):149-52. doi: 10.1159/000090391. PMID: 16374025.

Included multiple allergic conditions; outcomes not reported separately for asthma

Tsai YG, Chien JW, Chen WL, et al. Induced apoptosis of TH2 lymphocytes in asthmatic children treated with *Dermatophagoïdes pteronyssinus* immunotherapy. Pediatr Allergy Immunol. 2005 Nov;16(7):602-8. doi: 10.1111/j.1399-3038.2005.00313.x. PMID: 16238586.

Not an RCT and has no safety data

Tsai YG, Lai JC, Yang KD, et al. Enhanced CD46-induced regulatory T cells suppress allergic inflammation after *Dermatophagoïdes pteronyssinus*-specific immunotherapy. J Allergy Clin Immunol. 2014 Nov;134(5):1206-9 e1. doi: 10.1016/j.jaci.2014.06.005. PMID: 25065720.

Animals or in vitro; Study is about efficacy but does not have a comparator group or is not an RCT

Turkcapar N, Kinikli G, Sak SD, et al. Specific immunotherapy-induced Sjogren's syndrome. Rheumatol Int. 2005 Dec;26(2):182-4. doi: 10.1007/s00296-005-0606-x. PMID: 15965636.

Does not apply to any Key Question; Not allergic asthma

Valdivieso R, Iraola V, Estupinan M, et al. Bronchial asthma, sensitisation and exposure to Der p1 and Der f1 in an Andean Ecuadorian school. Allergol Immunopathol (Madr). 2010 Mar-Apr;38(2):100-2. doi: 10.1016/j.aller.2009.07.008. PMID: 20188454.

No original data; Does not include SCIT or SLIT

Valero A, Chivato T, Justicia JL, et al. Diagnosis and treatment of grass pollen-induced allergic rhinitis in specialized current clinical practice in Spain. Allergy Asthma Proc. 2011 Sep-Oct;32(5):384-9. doi: 10.2500/aap.2011.32.3480. PMID: 22195692.

Included multiple allergic conditions; outcomes not reported separately for asthma; Does not apply to any Key Question

Valovirta E, Berstad AK, de Blic J, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. Clin Ther. 2011 Oct;33(10):1537-46. doi: 10.1016/j.clinthera.2011.09.013. PMID: 21999887.

No allergic asthma; Other: design and rationale for another trial

Valovirta E, Jacobsen L, Ljorring C, et al. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy. 2006 Oct;61(10):1177-83. doi: 10.1111/j.1398-9952.2006.01190.x. PMID: 16942565.

Included multiple allergic conditions; outcomes not reported separately for asthma

Valovirta E. Effect of AIT in children including potential to prevent the development of asthma. Allergy. 2011 Jul;66 Suppl 95:53-4. doi:

10.1111/j.1398-9995.2011.02640.x. PMID: 21668856.

Not allergic asthma; No original data

Van Gysel D, Govaere E, Doli E, et al. Cockroach sensitisation in Belgian children. Eur J Pediatr. 2006 Sep;165(9):662-4. doi: 10.1007/s00431-006-0127-y. PMID: 16622661.

Does not include SCIT or SLIT

van Hemelen D, van Oosterhout AJ. Adjuvants for immunotherapy: lost in translation? Clin Exp Allergy. 2009 Dec;39(12):1783-5. doi: 10.1111/j.1365-2222.2009.03396.x. PMID: 20085594.

No original data

Varney VA, Edwards J, Tabbah K, et al. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy. 1997 Aug;27(8):860-7. PMID: 9291281.

Included multiple allergic conditions; outcomes not reported separately for asthma

Vaswani R, Garg A, Parikh L, et al. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. Ann Allergy Asthma Immunol. 2015 Sep;115(3):241-3. doi: 10.1016/j.anai.2015.06.018. PMID: 26195439.

Included multiple allergic conditions; outcomes not reported separately for asthma

Vaughn MP. Montelukast might improve compliance with subcutaneous immunotherapy treatments in patients with allergic asthma. J Allergy Clin Immunol. 2011 Jan;127(1):286; author reply -7. doi: 10.1016/j.jaci.2010.07.033. PMID: 20850867.

No original data

Ventura MT, Giuliano G, Buquicchio R, et al. Local and systemic reactions occurring during immunotherapy: an epidemiological evaluation and a prospective safety-monitoring study. Immunopharmacol Immunotoxicol. 2008;30(1):153-61. doi: 10.1080/08923970701620008. PMID: 18306111.

No type of immunotherapy specified

Verheggen BG, Westerhout KY, Schreder CH, et al. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. Clin Transl Allergy. 2015;5:1. doi: 10.1186/s13601-015-0045-z. PMID: 25691953.

Not allergic asthma; No original data

Verhoef A, Alexander C, Kay AB, et al. T cell epitope immunotherapy induces a CD4+ T cell population with regulatory activity. PLoS Med. 2005

Mar;2(3):e78. doi: 10.1371/journal.pmed.0020078. PMID: 15783262.

Does not apply to any Key Question

Vesna TS, Denisa D, Slavenka J, et al. Efficacy of Sublingual Immunotherapy with Dermatophagoides Pteronyssinus: A Real-life Study. Iran J Allergy Asthma Immunol. 2016 Apr;15(2):112-21. PMID: 27090364.

Included multiple allergic conditions; outcomes not reported separately for asthma

Vieths S, (2012). [Allergies]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz, 55(3), #Pages#

No original data

Vourdas D, Syrigou E, Potamianou P, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy. 1998 Jul;53(7):662-72. PMID: 9700035.

Included multiple allergic conditions; outcomes not reported separately for asthma

Wahn U, Klimek L, Ploszczuk A, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2012 Oct;130(4):886-93 e5. doi: 10.1016/j.jaci.2012.06.047. PMID: 22939758.

Included multiple allergic conditions; outcomes not reported separately for asthma

Wang CM, Chuang JJ. Effect of mite allergen immunotherapy on the altered phenotype of dendritic cells in allergic asthmatic children. Ann Allergy Asthma Immunol. 2013 Feb;110(2):107-12. doi: 10.1016/j.anai.2012.11.019. PMID: 23352530.

Study is about efficacy but does not have a comparator group or is not an RCT

Warner JO. In this issue. Volume 20 Issue 5 (August 2009). Pediatr Allergy Immunol. 2009 Aug;20(5):406-7. doi: 10.1111/j.1399-3038.2009.00931.x. PMID: 19674348.

No original data

Wei W, Liu Y, Wang Y, et al. Induction of CD4+CD25+Foxp3+IL-10+ T cells in HDM-allergic asthmatic children with or without SIT. Int Arch Allergy Immunol. 2010;153(1):19-26. doi: 10.1159/000301575. PMID: 20357481.

Does not apply to any Key Question

Weiner JM. Allergen injection immunotherapy. Med J Aust. 2006 Aug 21;185(4):234. PMID: 16922673.

No original data

Wen CJ, Zhu MF, Ren WM, Liu XY, Qian H, (2011). [Clinical efficacy and safety of sublingual immunotherapy using standardized Dermatophagoides farinae extract for children with combined allergic rhinitis and asthma syndrome]. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery, 46(5), #Pages#

Included multiple allergic conditions; outcomes not reported separately for asthma

Winther L, Arnved J, Malling HJ, et al. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. Clin Exp Allergy. 2006 Mar;36(3):254-60. doi: 10.1111/j.1365-2222.2006.02340.x. PMID: 16499635.

Included multiple allergic conditions; outcomes not reported separately for asthma

Wood RA, Togias A, Wildfire J, et al. Development of cockroach immunotherapy by the Inner-City Asthma Consortium. J Allergy Clin Immunol. 2014 Mar;133(3):846-52 e6. doi: 10.1016/j.jaci.2013.08.047. PMID: 24184147.

Included multiple allergic conditions; outcomes not reported separately for asthma

Worm M, Lee HH, Kleine-Tebbe J, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. J Allergy Clin Immunol. 2011 Jan;127(1):89-97, e1-14. doi: 10.1016/j.jaci.2010.11.029. PMID: 21211644

Does not apply to any Key Question; Mixed population

Wu Y, Long Z, Huang Y, Huang X, (2011). [Study on safety of standardized specific mite-allergen immunotherapy to children with allergic rhinitis and/or asthma]. Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery, 25(14), #Pages#

Included multiple allergic conditions; outcomes not reported separately for asthma

Yalcin AD, Gumuslu S, Parlak GE, et al. Systemic levels of ceruloplasmin oxidase activity in allergic asthma and allergic rhinitis. Immunopharmacol Immunotoxicol. 2012 Dec;34(6):1047-53. doi: 10.3109/08923973.2012.697902. PMID: 22737977.

Other: there are asthmatics treated with omalizumab; SIT only in AR

Ye YM, Lee SK, Kim SH, et al. Changes of serum cytokines after the long term immunotherapy with Japanese hop pollen extracts. J Korean Med Sci. 2006 Oct;21(5):805-10. doi: 10.3346/jkms.2006.21.5.805. PMID: 17043410.

Mixed population

Yepes-Núñez JJ, Gómez C, Espinoza Y, Cardona R, (2015). [The impact of subcutaneous immunotherapy with Dermatophagoides farinae and Dermatophagoides pteronyssinus on the quality of life of patients with allergic rhinitis and asthma]. Respiratory Care, 60(#issue#), 269-278

Other; not outcomes of interest (measures QOL using SF36)

Yukselen A, Kendirli SG, Yilmaz M, et al. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. Asian Pac J Allergy Immunol. 2013 Sep;31(3):233-41. doi: 10.12932/ap0276.31.3.2013. PMID: 24053706.

Included multiple allergic conditions; outcomes not reported separately for asthma

Zakzuk J, Jimenez S, Cheong N, et al. Immunological characterization of a Blo t 12 isoallergen: identification of immunoglobulin E epitopes. Clin Exp Allergy. 2009 Apr;39(4):608-16. doi: 10.1111/j.1365-2222.2008.03193.x. PMID: 19226278.

Animals or in vitro

Zhang X, Li MR, Wang C, Wang XN, Zhang HL, Lin J, Jin K, Li YC, (2010). [Clinical efficacy of a standardized specific immunotherapy against house dust mite in 85 asthmatic children]. Zhonghua er ke za zhi = Chinese journal of pediatrics, 48(7), #Pages#

Study is about efficacy but does not have a comparator group or is not an RCT;

Zidarn M, Košnik M, Šilar M, et al. Sustained effect of grass pollen subcutaneous immunotherapy on suppression of allergen-specific basophil response: A real-life, nonrandomized controlled study. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70(5):547-55.

Included multiple allergic conditions; outcomes not reported separately for asthma; Study is about efficacy but does not have a comparator group or is not an RCT

Appendix D: KQ1- What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

KQ1- What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

Table 1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ² Europe	SCIT Placebo	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT $IgE \geq 2$	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	Bousquet, 1985 ³ France	SCIT Placebo	Asthma diagnosis criteria- pulmonary tests (reversible bronchoconstriction to B agonist or significant sensitivity to methacholine and positive BPT with Dp) Severity NS Control status NS (baseline FEV1 required to be within 20% predicted)	SPT and IgE Positive SPT (clinic specific) $IgE RAST class 3-4$	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Ameal, 2005 ⁴ Europe	SCIT Placebo	Asthma diagnosis criteria GINA Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal size (10HEP)	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Vidal, 2011 ⁵ Europe	SCIT Placebo	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal > 3mm; $IgE \geq \text{class 2}$	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter)	Clinic
	Olsen, 1997 ⁶ Europe	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE NS	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Kohno, 1998 ⁷ Asia	SCIT Placebo	Asthma diagnosis criteria -Bronchial response to histamine Severity NS Control status -Controlled (no need of ICS)	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (Dfar)	Clinic
	Chakraborty, 2006 ⁸ Asia	SCIT Placebo	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE wheal >3mm	Monosensitized Grass (P sylvestris)	Single allergen Grass (P sylvestris)	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Creticos, 1996 ⁹ US	SCIT Placebo	Asthma diagnosis criteria Methacholine challenge Severity moderate to severe Control status uncontrolled (dependent of ICS)	SPT NS	Monosensitized Ragweed	Single allergen Ragweed	Clinic
	Ohman, 1984 ¹⁰ US	SCIT Placebo	Asthma diagnosis criteria- positive bronchial challenge to cat Severity NS Control status -Controlled (no need of ICS)	SPT NS	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Van Metre, 1988 ¹¹ US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +2 IgE significant	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Garcia-Ortega, 1993 ¹² Europe	SCIT Pharmacotherapy	Asthma diagnosis criteria-- positive bronchial challenge to dust mite Severity NS Control status NS	SPT and IgE SPT NS IgE RAST class 2	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴ Europe	SCIT HDM Placebo	Asthma diagnosis GINA criteria Severity moderate persistent Control status NS	SPT and IgE positive SPT (>3 mm) and allergen-specific IgE class 2	Polysensitized (72% of patients were sensitized to Timothy, 65% to dog, 52% to cat and 35% to birch pollen)	Single allergen Dust mite	Clinic
Mixed age	Wang, 2006 ¹⁵ Asia	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE NS	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Maestrelli, 2004 ¹⁶ Europe	SCIT Placebo	Asthma diagnosis criteria NS Severity mild to moderate per GINA Control status – NS (excluded if FEV1<70, 2+ asthma attacks in past 12m)	SPT and IgE SPT NS IgE class 3	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Ibero, 2006 ¹⁷ Europe	SCIT Placebo	Asthma diagnosis per mild moderate criteria Severity mild and moderate Control status NS	SPT and IgE	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Van Bever 1992 ¹⁸ Europe	SCIT Placebo	Asthma diagnosis criteria-(FEV >70%) Severity All severities Control status stable	SPT and IgE RAST	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (HDM)	Clinic
	Altintas,1999 ¹⁹ Asia	SCIT vs SCIT vs Placebo	Asthma diagnosis criteria NS Severity Mild to moderate Control status – Poorly controlled	SPT and IgE	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (Dpter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Hill, 1982 ²⁰ Australia	SCIT (rush) VS. Placebo	Asthma diagnosis criteria NS Severity NS Control status NS	SPT and IgE NS	Polysensitized and Monosensitized All patients sensitized to Grass (Rye) 18 patients also to Dust mite (D.pter)	Single allergen Grass (Rye)	Clinic
	Valovirta, 1984 ²¹ Valovirta, 2006 ²² US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +3 IgE class 2	Polysensitized Birch, Timothy, Cladosporium, HDM, cat	Single allergen Dog	Clinic
	Bousquet, 1988 ²³ France	SCIT Pharmacotherapy	Asthma diagnosis criteria- pulmonary tests (reversible bronchoconstriction to B2 and positive BPT) Severity NS Control status NS	SPT and IgE Positive SPT (clinic specific) IgE RAST class 3-4	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (Dpter)	Clinic
	Baris, 2014 ²⁴ Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria (FEV changes) Mild and moderate Control status NS	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (HDM)	Clinic
	Kilic, 2011 ²⁵ Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT > 3mm	Monosensitized Molds	Single allergen Molds Alternaria	Not specified
	Lozano, 2014 ²⁶ Europe	SCIT Pharmacotherapy	Asthma diagnosis not reported Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	Zielen, 2010 ²⁷ Europe	SCIT Pharmacotherapy (ICS alone)	Asthma diagnosis criteria GINA Severity NS Well controlled	SPT and IgE SPT >5mm; IgE of class 2 or greater (10.7 kU/l)	Polysensitized pollen, animal, house dust mite (Dpter-D far), and mold allergens	Single allergen Dust mite (Dpter)	Clinic
	Pifferi, 2002 ²⁸ Europe	SCIT No treatment	Asthma diagnosis per doctor criteria Severity NS Control status NS	SPT SPT (EAACI)	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Dreborg, 1986 ²⁹ Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE SPT 2 + IgE RAST class 1 or greater	Monosensitized Cladosporium	Single allergen Cladosporium	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Hui, 2014 ³⁰ Asia	SCIT OTHER (desensitization vaccine)**	Asthma diagnosis per Breathing Group of Pediatric Academy; Chinese Medical Association Mild persistent Control status NS	SPT and IgE SPT "positive" and/or allergen-specific IgE in serum (>0.35kUA/l)	Monosensitized Dust mite (DPter)	Single allergen Dust mite (Dpter)	Not specified
	Arroabarren, 2015 ³¹ Europe	SCIT SCIT (3 vs 5 y)	GINA criteria Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-Dfar) And Polysensitized (latex, food, tree, grass, weed, mold, cat, dog)	Single allergen Dust mite (Dpter)	Clinic
Children	Adkinson, 1997 ³² Limb, 2006 ³³ US	SCIT Placebo	Asthma diagnosis physician diagnosed Severity Moderate to severe Control status – Controlled (stable dose of ICS)	SPT and IgE	Polysensitized Dust mite (Dpter -Dfar) Trees (white oak) Weeds (ragweed, English plantain), Grass (Grass mix, Bermuda grass) Molds (Alternaria, aspergillus, cladosporium)	Multiple allergens	Clinic
	Alzakar, 2010 ³⁴ Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA and EPR Excluded severe asthma Control status NS	SPT and IgE Wheal > 3mm; Allergen specific IgE of 0.35 EU/mL	Polysensitized Alternaria, Cladosporium, Penicillium, grass mix, feather mixture, dog, horse, cat, Aspergillus, Fagacae, Betulaceae, plantain, Bermuda grass, Chenopodium, mugwort, Oleaceae and dust mite (Dpter-Dfar)	Multiple allergens	Clinic
	Tsai, 2010 ³⁵ Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA Severity moderate and severe persistent Control status NS	SPT and IgE Not specified	Monosensitized Dust mite (Dpter-Dfar)	Single allergen Dust mite (Dpter-Dfar)	Clinic

SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

* Authors did not report sensitization status

** the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table 2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	64	SCIT Placebo	24 +/- 9 24 +/- 8	47/53 37/63	32/5 32/5	NR
	Bousquet, 1985 ³		SCIT (Rush) Placebo	29 +/- 5 (Range 18-41) 27 +/- 6 (Range 19-42)	65/35 70/30	20/0 10/0	
							6.3 9.1

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
All ages	Ameal, 2005 ⁴	63	SCIT Placebo	23 (14-48)	47/53	32/3 31/5	NR
	Vidal, 2011 ⁵	45	SCIT Placebo	26 (14-42) 28 (16-52)	57/43 58/42	21/2 24/1	NR
	Olsen, 1997 ⁶	31	SCIT Placebo	32 (Range 18-56) 40.7 (Range 22-64)	NR	NR	NR
	Kohno, 1998 ⁷	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR
	Chakraborty, 2006 ⁸	14	SCIT Placebo	32.22 32.59	NR	8/0 6/0	NR
	Creticos, 1996 ⁹	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
	Ohman, 1984 ¹⁰	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
	Van Metre, 1988 ¹¹	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
	Garcia-Ortega, 1993 ¹²	36	SCIT Pharmacotherapy	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴	54	SCIT HDM Placebo	29 +/- 11 28 +/- 7	42/58 39/61	26/6 28/6	14.8 14.1
Mixed age	Wang, 2006 ¹⁵	132	SCIT Placebo	Range 6-45	56/44 61/39	64/2 65/1	7.1 +/- 0.81 7.3 +/- 0.79
	Maestrelli, 2004 ¹⁶	95	SCIT Placebo	20 +/- 8 23 +/- 10	61/39 71/29	41/8 31/15	1
	Ibero, 2006 ¹⁷	30	SCIT Placebo	10 (8-15) 12 (8-16)	66/34 60/40	15/NR 15/NR	NR
	Van Bever, 1992 ¹⁸	18	SCIT Placebo	9 (7-11) 12 (8-22)	NR	9/0 9/2	NR
	Altintas, 1999 ¹⁹	35	Aluminum Hydroxide SCIT Calcium Phosphate SCIT Aqueous SCIT Placebo	10.8 +/- 3.7 10.0 +/- 3.7 11 +/- 4 11 +/- 3	80/20 60/40 55/45 60/40	10/ NR 10/ NR 9/ NR 5/ NR	NR
	Hill, 1982 ²⁰	20	SCIT Placebo	Range 9-14 Range 9-14	Entire study 65/35	11/NR 9/NR	3 3
	Valovirta, 1984 ²¹ Valovirta, 2006 ²²	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
	Bousquet, 1988 ²³	215	SCIT (Rush) Pharmacotherapy	24 +/- 13(Range 3-72) 24 +/- 11(Range 3-72)	Entire study 68.0/32.0	171/NR 44/NR	12 9.8
	Baris, 2014 ²⁴	55	SCIT + Vit D SCIT alone Pharmacotherapy	9.2 +/- 2 8.8 +/- 1 7.9 +/- 3	38/62 47/53 50/50	17/0 15/0 18/0	NR
	Kilic, 2011 ²⁵	24	SCIT Pharmacotherapy	10.1 +/- 2.2 (7-13) 10.1 +/- 2.1 (8-14)	NR	12/3 12/5	NR
	Lozano, 2014 ²⁶	43	SCIT Pharmacotherapy	Median 9 (6-12) Median 9 (6-12)	48/52 55/45	21/1 20/2	1

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease
	Zielen, 2010 ²⁷	66	SCIT Pharmacotherapy (ICS alone)	Median 9 (6-17) Median 11 (6-16)	66/34 69/31	33/0 33/4	2
	Pifferi, 2002 ²⁸	29	SCIT Control	11 +/- 3 10 +/- 2	Entire Study 55/45	15/0 14/4	NR
	Dreborg, 1986 ²⁹	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
	Hui, 2014 ³⁰	90	SCIT Desensitization vaccine*	10.1 +/- 2.2 9.8 +/- 1.5	56/44 49/51	43/5 45/4	3.5
Children	Adkinson, 1997 ³²	121	SCIT Placebo	9 +/- 2 9 +/- 2	80/20 76/24	61/8 60/3	> 1 > 1
	Alzakar, 2010 ³⁴	242	SCIT Pharmacotherapy	9.8 +/- 1.7 (7-12) 10 +/- 1.5 (7-12)	55/45 60/40	105/20 137/25	NR
	Tsai, 2010 ³⁵	40	SCIT Pharmacotherapy	8.6 +/- 2.9 8.3 +/- 2.4	70/30 35/65	20/0 20/0	6 months

NR: Not reported * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table 3 – Intervention Characteristics SCIT

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	SCIT Placebo	Both (B2 and ICS)	0.1, 0.3 and 0.5 ml for weekly for 3 weeks and then 0.5 ml monthly	NR	Monthly for 12 months	35 µg /ml D. pter + 28 µg /ml D. far	54 weeks
	Bousquet, 1985 ³	SCIT Rush Placebo	NR	3000 BU (=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks not clearly stated)
	Ameal, 2005 ⁴	SCIT Placebo	Only rescue (B2)	0.5 mL of 70 µg/mL	NR	Monthly	14.25 µg of Der p 1/ml and 8.61 of Der p 2	12 months
	Vidal, 2011 ⁵	SCIT Placebo	Both (NS)	0.8ml	NR	Monthly	4.8 µg DP1, 3.2 µg DP2	4 months
	Olsen, 1997 ⁶	SCIT dust mite alum-precipitated Placebo	Only rescue medication	100000 SQ-U (after 15 weeks)	NR	3 weeks for one dose; every 6 weeks thereafter	7 µg Der p 1 or 10 µg Der f 1	1 year
	Kohno, 1998 ⁷	SCIT dust mite Rush Bronchodilators	conventional therapy	0.15-0.30 ml of 1/10 wt/vol	NR	Weekly for 2 months then every 2 weeks for 6 months	1 mg dust mite extract = 9.8 ng of major allergens Der1 and Der2 (5.4 ng was D far)	6 months
	Chakraborty, 2006 ⁸	SCIT Placebo	NR	1:2500 wt/vol	NR	Conventional Weekly	0.5 µg	2 years
	Creticos, 1996 ⁹	SCIT Ragweed Placebo	Only rescue medication	0.5 mL of 1:10 dilution (actual mean dose in year = 4 µg of Amb a1)	NR	Every 2 weeks for 3 months thereafter every 4 weeks	10 µg of Amb a1	2 years

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
	Ohman, 1984 ¹⁰	SCIT Cat Placebo	NR	0.3 ml of extract containing 13 units of cat allergen 1per ml or 300 µg/ml of cat albumin)	10.9 units cat allergen or 272 µg of cat albumin	Weekly	13 units of cat allergen 1 U/ml or 300 µg /ml of cat albumin)	6 weeks
	Van Metre, 1988 ¹¹	SCIT Cat Placebo	conventional therapy	1.0 mL of 4 .56 FDA units of Fel d 1 per mL.	NR	Biweekly	4 .56 FDA units of Fel d 1	At least 1 year
	Garcia-Ortega, 1993 ¹²	SCIT Dust mite Cluster Pharmacotherapy	conventional therapy (bronchodilators/usual care)	1000000 SQ	2000000 SQ	Every 15 days	NR	7 months
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴	SCIT HDM Placebo	Both Salbutamol and ICS)	100000 SQ-U w 6 weeks	20 SQ-U	Conventional	0.01ug	3 years
Mixed age	Wang, 2006 ¹⁵	SCIT dust mite alum-precipitated Placebo	Only rescue medication	100000 SQ-U	NR	6 weeks	9.8 µg Der p1	1 year
	Maestrelli, 2004 ¹⁶	SCIT dust mite Placebo	conventional therapy	7 BU (adults) 6 BU (children)	NR	every 3 weeks	6 µg /ml major antigens Der1 + Der2)	3 years
	Ibero, 2006 ¹⁷	SCIT Placebo	conventional therapy and rescue therapy	42.5 µg	216.75 µg	Monthly	NR	4 months
	Van Bever 1992 ¹⁸	SCIT Cluster Placebo	conventional therapy	1000 BU	16497 BU	Every 4 weeks	NR	1 year
	Altintas, 1999 ¹⁹	SCIT Dust mite Adsorbed Aluminum SCIT Dust mite Adsorbed calcium	NR	50000 -100000 SQ (targeted) 60000 to 100000 SQ (actual) 6 -10 IR 10 IR ≡ 1000w/v)	NR	Every 4 weeks	NR	2 years
	Hill, 1982 ²⁰	SCIT Rye grass Rush Placebo	conventional therapy (NS)	75-1000PNU = PNU of rye pollen	NR	Every 2 weeks until the start of the season; then every 4 weeks until the end of season	NR	8 months
	Valovirta, 1984 ²¹ Valovirta, 2006 ²²	SCIT Dog alum-precipitated Placebo	NR	100,000 SQ U Range from 8000 to 50000 in 4/15 subjects)	NR	6 weeks	NR	1 year
	Bousquet, 1988 ²³	SCIT Dust mite Pharmacotherapy	conventional therapy not specified	3000 BU	NR	Weekly for 6 weeks; then every 2 weeks for 1 year	NR	1 year

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Major Allergen Content	Duration of Treatment
	Baris, 2014 ²⁴	SCIT + Vit D SCIT alone Pharmacotherapy	Both	NR	NR	Buildup NS. Maintenance monthly	NR	2 months
	Kilic, 2011 ²⁵	SCIT Pharmacotherapy	conventional therapy (as part of study NS)	NR	NR	Buildup NS. Maintenance monthly	NR	12 months
	Lozano, 2014 ²⁶	SCIT Pharmacotherapy	Both (LTRA, LABA, ICS)	10,000 AUeq	NR	Monthly	4 µg Der p1, 15 µg Der p2	8 months
	Zielen, 2010 ²⁷	SCIT Pharmacotherapy (ICS alone)	Both (ICS)	0.6 mL of strength B= 10,000 TU/ml	NR	6 weeks	7 ug Der p 1 6 ug Der p 2	2 years
	Pifferi, 2002 ²⁸	SCIT HDM Control	conventional therapy not specified	800 U	24758.33 U (mean)	4 -6 weeks	NR	3 years
	Dreborg, 1986 ²⁹	SCIT Cladosporium Placebo	conventional therapy	100000 BU (reached after 18 weeks)	NR	Every 4 weeks	NR	10 months
	Hui, 2014 ³⁰	SCIT Desensitization vaccine*	Both (NS)	100,000 U/ml	1,025,000 U/ml	every 4-6 weeks	NR	51 weeks
Children	Adkinson, 1997 ³²	SCIT Placebo	conventional therapy and rescue therapy	4.3 µg Der p1- 5 µg Der f1- 26 µg Amb a1 38 µg group 1 0.7 mL of concentrate	NR	Biweekly for 24 months, every 3 weeks after 24 months	common dust mites, short ragweed, grass mix (timothy, orchard, perennial ryegrass) alternaria alternata, Bermuda grass, English plantain, white oak, cladosporium herbarum, aspergillus fumigatus	27 months
	Alzakar, 2010 ³⁴	SCIT Pharmacotherapy	conventional therapy (beclomethasone + aminophylline as part of study)	0.5 of stock standardized extracts	NR	Every 15 days then every 4-6 weeks	Single or multiple allergen SCIT (HDM, grass, trees, mold, pets)	12 months
	Tsai, 2010 ³⁵	SCIT Pharmacotherapy	Both (SABA, LTRAs, ICS, LABAs and oral corticosteroids) modified in stepwise manner per GINA guidelines	initial dose of 0.5 AU/mL weekly and increased 25-100% weekly until optimal maintenance dose reached	NR	Biweekly	Dp and Df (10,000 AU/mL)	3 months

NR: Not reported

BU: Biological units

SQU: standard quality units

PNU: Protein Nitrogen Unit

AU Allergy unit

µg: microgram

Ag/ml: major protein unit

TU: Treatment units

wt/vol Weight to volume

SE: Specific units of short-term immunotherapy

LTRA: Leukotriene receptor antagonist

LABA:Long acting Beta agonist SABA:Short acting Beta agonist

*the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table 4 – Asthma control

No study reported on Asthma control using ACT, ACQ or P-ACT scores

Table 5 – Quality of Life**Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (AQLQ)**

No study reported on Asthma QOL using Pediatric Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (PAQLQ)- School/Work Absences

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Value pre	Value post	Comparative Values
Kilic, 2011 ²⁵	Alternaria Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	Median (IQR) 3.8 (2.73-5.21) 4.91 (3.91-5.82)	Median (IQR) 6.52 (5.78-7) 5.86 (4.21-7)	SCIT pre vs post <i>P</i> = 0.002 Control pre vs post <i>P</i> =0.01 SCIT vs Control post <i>P</i> = 0.09
Lozano, 2014 ²⁶	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	4.9 5.14	6.4 5.42	SCIT vs Pharm post <i>P</i> =0.488
Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	Dust mite Mild asthma	SCIT Placebo	32 32	54 weeks	Median 22 23	Median (IQR) 7.44 [5.78-9.11] 11.44 [9.67-13.22]	SCIT vs placebo post % improvement 34.95 (<i>P</i> = 0.043) ¹
Amel, 2005 ⁴	Dust mite Mild and moderate	SCIT Placebo	29 26	12 months	Median (IQR) 17 [13-30] 27 [15-36]	Median (IQR) 4 [1-8] 10.50 [5-17]	SCIT vs placebo post <i>P</i> = 0.0025

NR: Not reported NS: Not significant

Table 6 – Medication Use**A. Quick Relief Medications**

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Olsen, 1997 ⁶	Dust mite Severity NS	SCIT Placebo	16 15	12 months	Asthma rescue medication consumption (inhaled beta-2 agonists) Mean number of puffs per week (percentage decrease)	27 52	14 (46%) 46 (NR)	SCIT pre post <i>P</i> <0.05 Placebo pre vs post <i>P</i> NS

NR: Not reported

NS: Not significant

SCIT vs placebo post data unless otherwise noted

B. Long term Control Medications

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	Dust mite Mild asthma	SCIT Placebo	32 32	54 weeks	Inhaled corticosteroids (beclomethasone), Weeks free of inhaled corticosteroids per patient	NR	Median-IQR 13 [3.5-30.5] 6 [1-18.5]	SCIT vs placebo pre vs post $P < 0.001$
Olsen, 1997 ⁶	Dust mite Severity NS	SCIT Placebo	16 15	12 months	Inhaled steroid consumption Mean number mg per week (percentage decrease)	4.7 1.4	2.9 (38%) 2.6 (NR)	SCIT pre vs post $P < 0.05$ Placebo pre post P NS
Baris, 2014 ²⁴	Dust mite Mild and moderate	SCIT + Vit D SCIT alone Pharmacotherapy	17 15 18	12 months	Inhaled corticosteroids Rate of discontinuation	NA	3 (20%) 6 (35%) 0 (0)	SCIT with and without vitD vs pharmacotherapy alone $P=0.002$
Lozano, 2014 ²⁶	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	Inhaled corticosteroids Changes in the need for medication	N (%) 7 (33) 5 (25)	N (%) 4 (18) 5 (25)	NR
					LTRA's Changes in the need for medication	N (%) 7 (33) 5 (25)	N (%) 4 (18) 5 (25)	SCIT pre vs post $P < 0.046$ Pharmacotherapy pre post $p=0.158$
					IC + LTRA Changes in the need for medication	N (%) 2 (10) 1 (5)	N (%) 1 (5) 1 (5)	NR
					IC + LABA Changes in the need for medication	N (%) 1 (5) 1 (5)	N (%) 1 (5) 3 (15)	NR
Hui, 2014 ³⁰	Dust mite Mild asthma	SCIT desensitization vaccine*	43 45	3 years	Steroids dose Budesonide equivalents (µgs)	196.7 +/- 65.6 206.7 +/- 45	71.3 +/- 53.8 101.3 +/- 48.5	SCIT vs vaccine pre $P = 0.081$ SCIT vs vaccine post $P = 0.027$
Adkinson, 1997 ³²	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	Use of inhaled steroids (number of days in previous 60 days)	21.4 +/- 26 20.1 +/- 24.9	Change: -10.1 +/- 24 -5.4 +/- 27.8	SCIT pre vs post $P < 0.001$ Placebo pre vs post $P = 0.16$ Mean difference in change (SCIT vs placebo) = 4.7 (95% CI -4.7 to 14) $P = 0.26$

NR: Not reported NS: Not significant

SCIT vs placebo post data unless otherwise noted

LTRA: Leukotriene receptor antagonist

LABA: Long acting Beta agonist

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

C. Systemic Corticosteroids

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Pifferi, 2002 ²⁸	Dust mite Severity NS	SCIT Control	15 14	3 years	systemic steroids (Days of therapy/year)	22 25	1 12	SCIT vs Control $p < 0.01$

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Adkinson, 1997 ³²	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	Use of oral steroids (number of days in previous 60 days)	5.3+/-13.3 4.4+/-10.8	-1.9+/-12.4 -1.7+/-12.1	SCIT pre vs. post $P= 0.19$ Placebo pre vs. post $P= 0.75$ Mean difference in change (placebo vs. SCIT)= 0.1 (95% CI -4.2 to 4.5) $P=0.49$

NR: Not reported NS: Not significant

SCIT vs placebo post data unless otherwise noted

Table 7 – Asthma Exacerbations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Zielen, 2010 ²⁷	Dust mite Severity NS	SCIT Pharmacotherapy (ICS alone)	32 33	2 years	Numbers of asthma exacerbations requiring oral steroids	NR	2 patients/ 2 events 1 patient/ 1 event	NR
Pifferi, 2002 ²⁸	Dust mite Severity NS	SCIT Control	15 14	3 years	Rate of asthma exacerbations per year	8 8.5	1 4.5	SCIT vs Pharm $P < 0.01$

NR: Not reported NS: Not significant

SCIT vs placebo post data unless otherwise noted

Table 8 – Healthcare Utilizations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Tsai, 2010 ³⁵	Dust mite Moderate and severe	SCIT Pharmacotherapy	20 20	6 months	Outpatient visits Number of clinic visits in 6 months	NR	SCIT 17.25 +/- 4.6 Control: 12.4 +/- 5.87	Mean difference: SCIT vs Pharm 4.8, $P= 0.006$
					Number of ED visits or hospitalizations in 6 months			
Adkinson, 1997 ³²	Multiple Moderate to severe	SCIT vs. placebo	61 60	30 months	Number of office visits from baseline to follow up	0.05 +/- 0.28 0.03 +/- 0.18	Change: -0.03 +/- 0.38 0 +/- 0.26	SCIT pre vs. post: $P= 0.75$ Placebo pre vs post $P >0.99$ Mean difference change placebo vs. SCIT= 0.03 (95% CI -0.07 to 0.14) $P=0.71$
					Number of ED visits from baseline to follow up	0.08 +/- 0.33 0.03+/-0.18	Change: -0.05 +/- 0.38 -0.02+/-0.37	SCIT pre vs. post $P >0.53$ Placebo pre vs. post $P >0.99$ Mean difference change placebo vs. SCIT = 0.03 (95% CI -0.08 to 0.15) $P=0.73$

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
					Number of hospitalizations from baseline to follow up	0.11 +/- 0.64 0.2 +/- 0.90	Change: -0.11 +/- 0.64 -0.10 +/- 0.77	SCIT pre vs. post P=0.5 Placebo pre vs. post P=0.63 Mean difference change placebo vs. SCIT = 0.01 (95% CI -0.24 to 0.27) P= 0.43

NR: Not reported

NS: Not significant

SCIT vs placebo post data unless otherwise noted

Table 9 – Pulmonary Physiology**A. PEF**

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Maestrelli, 2004 ¹⁶	Dust mite Mild and moderate	SCIT Placebo	41 31	3 years	Morning PEF scores (% predicted)	95 97	104 101	SCIT pre vs post P<0.05 Placebo pre vs post NS
Wang, 2006 ¹⁵	Dust mite Mild to moderate	SCIT Placebo	56 61	12 months	Morning PEF (l/min)	289.6 +/- 9.94 308.4 +/- 12.6	309.5 +/- 9.29 330.1 +/- 10.4	SCIT pre vs post P=0.02 Placebo pre vs post P=0.01 SCIT vs Placebo pre P=0.26 SCIT vs Placebo post P=0.14
					Evening PEF (l/min)	293.1 +/- 10.6 316 +/- 12.1	312.2 +/- 9.27 335.1 +/- 10.7	SCIT pre vs post P=0.02 Placebo pre vs post P=0.02 SCIT vs Placebo pre P=0.16 SCIT vs Placebo post P=0.11
Kohno, 1998 ⁷	Dust mite Severity NS	SCIT Rush Bronchodilators	8 6	6 months	Morning PEF (L/min)	471.2 +/- 27.3 484.3 +/- 30.5	506.2 +/- 25.2 491.1 +/- 26.8	SCIT pre vs post P < 0.03 B2 pre vs post P NS
Zielen, 2010 ²⁷	Dust mite Severity NS	SCIT + ICS ICS alone	32 33	2 years	Increase in morning PEF (L/min)	NR	Change from baseline (% +/- SD) +55 (49) +30 (44)	SCIT vs ICS alone P <0.05
					Mean PEF +/- SD (L/min)	296 +/- 101 315 +/- 91	315 +/- 116 345 +/- 95	SCIT vs ICS P =0.0315
Hui, 2014 ³⁰	Dust mite Mild asthma	SCIT Desensitization Vaccine*	43 45	3 years	Mean PEF	Mean +/- SD 63.3 +/- 5.4 62.3 +/- 5.1	91.3 +/- 5.8 81.6 +/- 4.5	SCIT pre vs post P = 0.007
Dreborg, 1986 ²⁹	Cladosporium Mild to moderate	SCIT Placebo	16 14	6 months	Mean PEF	290 310	280 340	SCIT vs Placebo P NS
Kilic, 2011 ²⁵	Alternaria Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	PEF (%) Median IQR	76 [64-91] 74 [57-93]	96 [81-102] 101 [73-106]	SCIT pre vs post P=0.007 Pharm pre vs post P=0.02 SCIT vs pharm P=0.2

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Adkinson 1997 ³²	Multiple Moderate to severe	SCIT Placebo	61 60	30 months	PEF (% predicted)	81.9 ± 10.8 84.8 ± 8.6	(change from baseline) 2.5 ± 11.1 -1.4 ± 11.1	SCIT vs placebo Mean difference (95% CI) P Baseline: 2.9 (0.6 to 6.4), P=0.17 Change: -3.8 (-7.8 to 0.1), P=0.05
Creticos, 1996 ⁹	Short ragweed Moderate to severe	SCIT Placebo	11 11	Year 2	Mean daily PEF during peak season (l/min)	454 444	480 +/-12 461 +/-13	SCIT vs Placebo post P=0.03
Tsai, 2010 ³⁵	Dust mite Moderate to severe	SCIT Pharmacotherapy	20 20	6 months	PEF (% of predicted value)	83.15 ± 7.49 84.98 ± 5.5	84.3 ± 5.56 84.12 ± 4.72	Change pre vs post SCIT 1.15, P =0.056 Pharm -0.86, P = 0.099 Mean difference SCIT vs pharm At baseline -1.83, P = 0.39 At follow-up: 0.18, P = 0.92

NS: Not significant SCIT vs placebo post data unless otherwise noted

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

B. FEV₁

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Wang, 2006 ¹⁵	Dust mite Mild to moderate	SCIT Placebo	64 65	12 months	FEV1 (% predicted)	87.96 ±1.43 87.97 ±1.74	NR NR	SCIT pre vs post P NS Placebo pre vs post P NS
Chakraborty, 2006 ⁸	Dust mite Severity NS	SCIT Placebo	8 6	2 years	FEV1 (% predicted)	Mean 78.56 74.5	Mean 92.61 78.91	SCIT pre vs post P <0 .001 Placebo pre vs post P >0.05
Lozano, 2014 ²⁶	Dust mite Mild and moderate	SCIT Pharmacotherapy	21 20	8 months	FEV1 (percentage of patients with FEV >80%)	99.01 99.1	NR	At 8-month, 100% of patients had an FEV1 >80%
Bousquet 1988 ²³	Dust mite Severity NS	SCIT – Rush Pharmacotherapy	125 25	12 months	FEV1 (% predicted values) Mean +/- SD	82.3 +/- 23.2 85.6 +/- 26.1	98.6 +/- 16.3 83.4 +/- 18.9	SCIT pre vs post P <0.0001 Pharm pre vs post P NS SCIT vs B2 (post) P<0.0001
Kilic, 2011 ²⁵	Alternaria Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	FEV1 Median – IQR	73 [60-80] 75 [65-97]	96 [83-119] 85 [80-117]	SCIT pre vs post P= 0.008 Pharm pre vs post P= 0.02 SCIT vs pharm P= 0.009
Alzakar, 2010 ³⁴	Multiple allergens Excluded severe asthma	SCIT Pharmacotherapy	85 112	12 months	FEV1 - Patients with improvement in pulmonary function test	NR	51/85 (60%) 21/112 (19%)	SCIT vs pharmacotherapy P=0 .0001

NR: Not reported

NS: Not significant

SCIT vs placebo post data unless otherwise noted

C. FVC

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Wang, 2006 ¹⁵	Dust mite Mild to moderate	SCIT Placebo	64 65	1 year	FVC	94.15 +/-1.39 95.17 +/-1.71	NR NR	SCIT pre vs post P NS Placebo pre vs post P NS

NR: Not reported

NS: Not significant

SCIT vs placebo post data unless otherwise noted

Table 10 - Airway Hyperresponsiveness (AHR)**A. Methacholine Challenge**

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Maestrelli, 2004 ¹⁶	Dust mite Mild and moderate	SCIT Placebo	41 31	3 years	AHR- PD20 FEV1	μg methacholine (geometric mean (95%CI) 158 (91-274) 95 (44-203)	183 (104-322) 175 (101-305)	SCIT pre vs post = NS Placebo pre vs post = NS SCIT vs placebo post=NS <i>P</i> values not reported <i>P</i> values not reported
Pifferi, 2002 ²⁸	Dust mite Severity NS	SCIT Control	15 14	3 years	AHR- PD20 FEV1 (ug)	(μg methacholine, cumulative dose) 93.5 ± 56.3 374.3 ± 505.5	997.7±974.0 388.5±516.4	P-values are not reported for SCIT vs.control dose of methacholine The authors calculated the ratio of the incidence of “non- improvement” of bronchial reactivity in the SIT to the control group (Relative Risk: 0.3, and 95% CI between 0.11 and 0.87) indicated the likelihood of non-improvement of the former was 1/3 of that of the latter
Zielen, 2010 ²⁷	Dust mite Severity NS	SCIT + ICS ICS alone	32 33	2 years	AHR- PC20 FEV1	NR	NR	SCIT pre vs post NR Control pre vs post NR SCIT vs.control post: NR
Garcia-Ortega, 1993 ¹²	Dust mite Severity NS	SCIT Pharmacotherapy	18 18	7 months	AHR- PD20 FEV1	(Methacholine inhalatory units) 18±26 19±27	NR	SCIT pre vs post, <i>P</i> NS Pharm pre vs post NR SCIT vs control post, <i>P</i> =NS
Ohman, 1984 ¹⁰	Cats Severity NS	SCIT Placebo	9 8	17 weeks	AHR- PD 20 FEV1	Methacholine, Bronchoprovocation Units (Geometric Mean) 3.0 1.7	4.7 3.8	SCIT pre vs post, <i>P</i> NS Placebo pre vs post, <i>P</i> NS SCIT vs Placebo NR

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Adkinson, 1997 ³² Limb, 2006 ³³	multiple allergen Moderate to severe	SCIT Placebo	61 60	30 months	AHR- PC 20 FEV1	methacholine, µg/ml (geometric mean, 95% CI) 0.23 ± 1.33 0.32 ± 0.32	0.41± 1.87 0.39 ± 1.51 (change from baseline)	SCIT pre vs post $P= 0.008$ Placebo pre vs post $P=0.003$ SCIT vs Placebo post, $P > 0.99$
Kilic, 2011 ²⁵	Alternaria Mild and moderate	SCIT Pharmacotherapy	9 7	12 months	AHR- Methacholine challenge	Mean – IQR 0.49 [1.17-NR] 1.1 [1.52-NR]	Mean – IQR 4.07 [5.59-NR] 0.90 [2.53-NR]	SCIT pre vs post $P= 0.002$ SCIT vs pharm $P = 0.03$

NR: Not reported

NS: Not significant

PC20: Concentration of allergen causing a fall if 20% in FEV1

PD20: Dose of allergen causing a fall if 20% in FEV1

B. Allergen Challenge

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	Dust mite Mild asthma	SCIT Placebo	32 32	56 weeks	AHR- Allergen challenge PD20 FEV1	No units Mean – IQR 10.05 [5.48-81] 43.5 [6.1-511]	Mean – IQR 111.06 [41.05-686] 41 [3.35- 311]	SCIT pre vs post $P < 0.001$ Placebo pre vs post $P = 0.648$ SCIT vs placebo $P = 0.029$
Ameal, 2005 ⁴	Dust mite Mild and moderate	SCIT Placebo	29 26	12 months	AHR- Allergen challenge PD20 FEV1	HEP/ml Median – IQR 2.56 [0.54-5.61] 2.77 [1.69-4.02]	Median – IQR 7.14 [4.29-14.38] 2.76 [1.5-10.81]	SCIT pre vs post $P < 0.0001$ Placebo pre vs post $P = 0.9292$ SCIT vs placebo pre $P = 0.9173$ SCIT vs placebo post $P = 0.0029$
Bousquet 1985 ³	Dust mite Severity NS	SCIT Placebo	20 10	7 weeks	AHR- Allergen challenge (PD20 FEV1)	µg of allergen solution 96.3±82.1 79.1±93.6	432±171 95.0±99.8	SCIT, pre vs post, $P<0.01$ Placebo, pre vs post, $P=NS$ SCIT vs Placebo post $P<0.01$
Ibero, 2006 ¹⁷	Dust mite Mild and moderate	SCIT Placebo	15 15	4 months	AHR- Allergen challenge PC20 FEV1	HEP units llergen/ml Mean [IQR] 26 [9-43.2] 5.2 [2.6-7.8]	Mean [IQR] 309.4 [-39-657.8] 8 [2.6-13.4]	SCIT pre vs post $P = 0.0054$ Placebo pre vs post $P > 0.05$ SCIT vs. placebo, post p=0.0020
Olsen, 1997 ⁶	Dust mite Severity NS	SCIT Placebo	16 15	12 months	AHR- Allergen challenge (Dpt) PC 20 FEV1	SQ-Units/ml 25000 11000	37000 14000	SCIT, pre vs post, $P=0.022$ Placebo pre vs post, $P=0.60$ SCIT vs Placebo post, p=0.037
					AHR- Allergen challenge PC 20 FEV1	SQ-Units/ml 31000 29000	46000 20000	SCIT pre vs post, $P=0.039$ Placebo pre vs post, $P=0.75$ SCIT vs Placebo post, $P=0.041$
Van Bever 1992 ¹⁸	Dust mite All severities	SCIT Placebo	9 9	12 months	AHR- Allergen challenge PD 20 FEV1 Median PD 20 house dust mite (BU)	Median Biologic Units (BU) 238 303	477 385	SCIT pre vs post, $P=0.04$ Placebo, pre vs post, $P=0.11$ SCIT vs Placebo $P = 0.24$
Altintas,	Dust mite	SCIT-Adsorbed	10	2 years	BPT -Allergen	Geometric mean SQ/ml	31622	No significant difference among

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
1999 ¹⁹	Mild to moderate	aluminum SCIT-Adsorbed calcium SCIT-aqueous Placebo	10 9 5		bronchial provocation test)	7244 4786 2137 4786	39810 31153 7100	treatment groups, P>0.05 All SCIT vs Placebo P<0.05
Kohno, 1998 ⁷	Dust mite Severity NS	SCIT Pharmacotherapy (Bronchodilators NS)	8 6	6 months	AHR- Allergen challenge PC 20 FEV1	(wt/vol) Concentration of dust mite extract 1:303.7±1231: 230.0±154.5	1:65.0±13.2 1:291.7±158.9	SCIT pre vs post, P<0.03 Pharm pre vs post, P NS SCIT vs. control post, NR
Garcia-Ortega, 1993 ¹²	Dust mite Severity NS	SCIT Pharmacotherapy	18 18	7 months	Allergen bronchial provocation, PD-20 (inhalatory units; IU)	47±52 70±93	425±303 106±196	SCIT, pre vs post, P=0.01 Conventional pre vs post NS SCIT vs Conventional P=0.001
Ohman, 1984 ¹⁰	Cats Severity NS	SCIT Placebo	9 8	17 weeks	AHR- Allergen challenge PD 20 FEV1	BU geometric mean cumulative dose 4.27 8.8	20.7 12.3	SCIT pre vs post P <0.05 Placebo pre vs post, P NS SCIT vs Placebo,post P NS
Van Metre, 1988 ¹¹	Cats Severity NS	SCIT Placebo	11 11	12 months	AHR- Allergen challenge PD 20 FEV1 Cat extract PD 20 (Comparison of the median ratios values of the measurements from baseline to 1 year)	NR	2.8 0.80 Median ratio of allergen extract required for PD 20, post relative to pre treatment concentration	SCIT pre vs post NR Placebo pre vs post NR SCIT vs Placebo, P<0.01
Valovirta, 1984 ²¹ Valovirta, 1986 ²²	Dogs Severity NS	SCIT Placebo	15 12	12 months	Bronchial provocation test to dog dander extract	NR	40 17	SCIT, pre vs post, P<0.1 Placebo pre vs post NR SCIT vs Placebo, P=NS
Dreborg, 1986 ²⁹	Cladosporium Mild to moderate	SCIT Placebo	16 14	10 week period during peak season	AHR- Allergen challenge positive defined as peak expiratory flow reduction of at least 15%	NR NR	NR NR	SCIT pre vs post, P<0.01 Placebo pre vs post, <0.05 SCIT vs control P<0.05
Creticos, 1996 ⁹	Short ragweed moderate to severe	SCIT Placebo	11 11	2 Year	AHR- Allergen challenge PD 20 FEV1 Amount of allergen causing	Logarithm of allergen dose -1.4 +/- 1.1 -1.5 =/- 1.3	-0.273 ± 0.045 -0.662 ± 0.135	SCIT pre vs post NR Placebo pre vs post NR SCIT vs Control post , P=0.03

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
					20% drop in FEV1(PD 20)			

NR: Not reported

NS: Not significant

PC20: Concentration of allergen causing a fall if 20% in FEV1

PD20: Concentration of allergen causing a fall if 20% in FEV1

µg :migrogram

SCIT vs placebo post data unless otherwise noted

C. Exercise Challenge

There were no studies reporting on exercise challenge

Table 11 – Immunologic Parameters

A. IgE

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Gallego, 2010 ²	Dust mite (Dpter-Dfar)	SCIT Placebo	1 year	Specific IgE to Dpter (kUA/l)	Mean (SD) 44.8 (33.5) 49.6 (35.1)	Mean (SD) 39.5 (31.4) 43 (35)	SCIT pre vs post $P=0.06$ Placebo pre vs post $P=0.008$ SCIT vs placebo post NR
Hui, 2014 ³⁰	Dust mite (Dpter)	SCIT desensitization vaccine *	3 years	Specific IgE to Dpter (kUA/l)	Mean (SD) 91.4 (29.1) 92.6 (24.5)	Mean (SD) 77.6 (26.4) 90.8 (20.5)	SCIT vs placebo at year 3 $P=0.003$
Zielen, 2010 ²⁷	Dust mite (Dpter)	SCIT + ICS ICS alone	2 years	Specific IgE to Dpter (kU/L)	Geometric means 16.29 14.46	Decrease in geometric means -22.9% + 2%	SCIT+ ICS vs ICS alone post $P=0.0217$
Blumberga, 2011 ¹³	Dust mite (Dpter)	SCIT Placebo	1 year	Specific IgE to Dpter (Δ log)	NR	Change from baseline - 95% CI 0.048 [-0.017,-0.11] -0.051 [-0.11, -0.0080]	SCIT vs placebo post $P=0.028$
Tsai, 2005 ³⁶	Dust mite (Dpter)	SCIT Control	1 year	Dpt-specific IgE (kU/l)	70.8 (35.97) 61.18 (38.87)	52.36 (37.84) 56.32 (38.56)	SCIT vs pharm post $P < 0.005$
Vidal, 2011 ⁵	Dust mite (Dpter)	SCIT Placebo	15 weeks	Specific IgE to Dpter kU/L	Median [IQR] 50 [72.5-NR] 29.1 [81.3-NR]	Median [IQR] 49.7 [116.3-NR] 20.5 [58.7-NR]	Difference [IQR] SCIT pre - post -0.38 [28.9] Placebo pre-post 3.2 [8.7] SCIT vs placebo Baseline values $P=0.73$ Final values $P=0.26$ Differences $P=0.0425$
Kilic, 2011 ²⁵	Alternaria	SCIT Pharmacotherapy	12 months	Specific IgE to alternaria kU/L	Median [IQR] 26.4 [21.8-NR] 35.3 [19-NR]	Median [IQR] 8.17 [14.2-NR] 46.8 [28.4-NR]	SCIT pre vs post $P=0.004$ Pharm pre vs post $P=0.05$ SCIT vs pharm post $P = 0.0001$
Alzakar, 2010 ³⁴	Dust mites, mold, trees, animals, grass	SCIT Pharmacotherapy (Beclomethasone + Aminophylline)	12 months	Number of patients with reduction in specific IgE (≤ 0.35 IU/ml)	NR NR	64 (75%) 9 (8%)	SCIT vs pharmacotherapy post $P = 0.0001$

NR: Not reported

NS: Not significant

SCIT vs placebo post data unless otherwise noted

*the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

B. IgG4

Study	Allergen	Arms	Time of Measure	Outcome/ Unit	Baseline Values	Final Values	Comparative Values
Baris, 2014 ²⁴	Dust mites unspecified	SCIT + vitamin D SCIT alone VIt D alone	12 months	Der p 1 specific IgG4 Unit NR	Mean 0.13 0.12 0.05	Mean 4.23 2.8 0.09	Pre vs post within arm $P = 0.002$ $P = 0.002$ $P = 0.0002$ Between arms not reported
Vidal, 2011 ⁵	Dust mite (Dpter)	SCIT Placebo	15 weeks	Specific IgG4 to Dpter Unit NR	Median [IQR] 0.12 [0.11-NR] 0.10 [0.17-NR]	Median [IQR] 0.40 [0.76-NR] 0.10 [0.21-NR]	Difference [IQR] SCIT pre - post 0.21 [0.16] Placebo pre-post -0.02[0.25] SCIT vs placebo pre $P = 0.55$ SCIT vs placebo post $P = 0.001$ Differences $P = 0.0003$
Zielen, 2010 ²⁷	Dust mite (Dpter)	SCIT + ICS ICS alone	2 years	Specific IgG4 to Dpter Unit NR	NR	NR	SCIT vs ICS alone post Significantly increased $P < 0.0001$
Gallego, 2010 ³	Dust mite (Dpter-Dfar)	SCIT Placebo	1 year	Der p 1 specific IgG4 Unit NR	NR NR	NR NR	SCIT pre vs post DPter $P = 0.02$ Der p1 $P = 0.001$ Der p2 $P = 0.048$ Placebo pre vs post NR SCIT vs placebo NR
				Ratio of Specific IgE/Specific IgG4 (SD)	Median 94.8 (89.9) 103.3 (83)	Median 65.1 (54.3) 133 (204.6)	SCIT pre vs post $P = 0.02$ Placebo pre vs post NR

NR: Not reported NS: Not significant

SCIT vs placebo post data unless otherwise noted

C. Allergy Skin Testing

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Hui, 2014 ³⁰	Dust mite (Dpter)	SCIT Control*	3 years	SPT (skin prick testing)	Mean (SD) 1.2 (0.5) 1.3 (0.5) $P = 0.532$	SPT results remained unchanged	No differences between groups were identified
Vidal, 2011 ⁵	Dust mite (Dpter)	SCIT Placebo	15 weeks	Specific IgE to Dpter kU/L	Median [IQR] 50 [72.5-NR] 29.1 [81.3-NR]	Median [IQR] 9.7 [116.3-NR] 20.5 [58.7-NR]	Difference [IQR] SCIT pre vs post -0.38 [28.9] Placebo pre vs post 3.2 [8.7] SCIT vs placebo pre $P = 0.73$ SCIT vs placebo post $P = 0.26$ Differences $P = 0.0425$
				CTI Cutaneous tolerance index	NA	CTI -95% CI 2.81 [1.29-7.48] 1.03 [0.44-2.41]	SCIT vs placebo post Difference [95% CI] P 0.27 [0.11-0.56] $P < 0.05$

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Blumberga, 2011 ¹³	Dust mite (Dpter)	SCIT Placebo	3 years	Intradermal skin testing, Immediate-phase skin reactions	Mean 24 21	11 5	SCIT vs placebo at 3 years $P = 0.0002$
				Intradermal skin testing, Late-phase skin reaction	Mean 23 26	0 22	SCIT vs placebo at 3 years $P < 0.0001$
				Skin prick test titration HEP--the estimated HDM-allergen concentration that caused histamine equivalent skin reactions (HEP)	Mean 6 6	Mean 377 48	SCIT vs placebo at 3 years $P < 0.0001$
Alzakar, 2010 ³⁴	Dust mites, mold, trees, animals, grass	SCIT Pharmacotherapy (Beclomethasone + Aminophylline)	12 months	NR	NR NR	74 (87%) 8 (7%)	SCIT vs pharm post $P = 0.0001$
Gallego, 2010 ²	Dust mite (Dpter-Dfar)	SCIT Placebo	54 weeks	HEP (dose of native allergen extract needed to produce the same wheal size as the positive control for Skin prick testing	21.9 -0.31	NR NR	$P = 0.029$ NR

NR: Not reported NS: Not significant

SCIT vs placebo post data unless otherwise noted

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table 12. Compliance

Study	Allergen	Arms	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Adkinson, 1997 ³²	Multiple Moderate to severe	SCIT Placebo	30 months	Prescribed doses and doses recorded in diaries	NR	92.6% 93.6	Final comparative values NR

NR: Not reported NS: Not significant

Appendix E: KQ2- What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

KQ2- What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

SECTION A SCIT Safety for RCTs

Table A.1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ² Europe	SCIT Placebo	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT $IgE \geq 2$	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	Bousquet, 1985 ³ France	SCIT Placebo	Asthma diagnosis criteria- pulmonary tests (reversible bronchoconstriction to B agonist or significant sensitivity to methacholine and positive BPT with Dp) Severity NS Control status NS (baseline FEV1 required to be within 20% predicted)	SPT and IgE Positive SPT (clinic specific) $IgE RAST class 3-4$	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Ameal, 2005 ⁴ Europe	SCIT Placebo	Asthma diagnosis criteria GINA Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal size (10HEP)	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Vidal, 2011 ⁵ Europe	SCIT Placebo	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Wheal > 3mm; $IgE \geq \text{class 2}$	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter)	Clinic
	Kohno, 1998 ⁷ Asia	SCIT Placebo	Asthma diagnosis criteria -Bronchial response to histamine Severity NS Control status -Controlled (no need of ICS)	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dfar)	Single allergen Dust mite (Dfar)	Clinic
	Garcia-Ortega, 1993 ¹² Europe	SCIT (cluster) Pharmacotherapy	Asthma diagnosis criteria- positive bronchial challenge to dust mite Severity NS Control status NS	SPT and IgE SPT NS $IgE RAST class 2$	Monosensitized Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Chakraborty, 2006 ⁸ Asia	SCIT Placebo	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE wheal >3mm	Monosensitized Grass (P sylvestris)	Single allergen Grass (P sylvestris)	Not specified
	Creticos, 1996 ⁹ US	SCIT Placebo	Asthma diagnosis criteria methacholine challenge Severity moderate to severe Control status uncontrolled (dependent of ICS)	SPT Not specified	Monosensitized Ragweed	Single allergen Ragweed	Clinic
	Ohman, 1984 ¹⁰ US	SCIT Placebo	Asthma diagnosis criteria -positive bronchial challenge to cat Severity NS Control status -Controlled (no need of ICS)	SPT Not specified	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Van Metre, 1988 ¹¹ US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +2 IgE significant	Mono vs Polysensitized unclear* All patients sensitized to cat	Single allergen Cat	Clinic
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴ Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity moderate persistent Control status NS	SPT and IgE positive SPT (>3 mm) and allergen-specific IgE class 2	Polysensitized (72% of patients were sensitized to Timothy, 65% to dog, 52% to cat and 35% to birch pollen)	Single allergen Dust mite	Clinic
	Casanovas, 2005 ³⁷ Europe	SCIT modified. SCIT unmodified	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT >3mm	Monosensitized Timothy grass	Single allergen Timothy grass	Clinic
Mixed age	Ibero, 2006 ¹⁷ Europe	SCIT Placebo	Asthma diagnosis per mild moderate criteria Severity mild and moderate Control status NS	SPT and IgE	Monosensitized Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Lozano, 2014 ²⁶ Europe	SCIT Pharmacotherapy	Asthma diagnosis not reported Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	Baris, 2014 ²⁴ Asia	SCIT Pharmacotherapy	Asthma diagnosis GINA criteria (FEV changes) Mild and moderate Control status NS	SPT and IgE NS	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (HDM)	Single allergen Dust mite (HDM)	Clinic
	Zielen, 2010 ²⁷ Europe	SCIT Pharmacotherapy (ICS alone)	Asthma diagnosis criteria GINA Severity NS Well controlled	SPT and IgE SPT >5mm; IgE of class 2 or greater (10.7 kU/l)	Polysensitized pollen, animal, house dust mite (Dpter-D far), and mold allergens	Single allergen Dust mite (Dpter)	Clinic
	Altintas, 1999 ¹⁹ Asia	SCIT SCIT Placebo	Asthma diagnosis criteria NS Severity Mild to moderate Control status – Poorly controlled	SPT and IgE Values for baseline and follow-up	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Schubert 2009 ³⁸ Europe	SCIT cluster SCIT conventional	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE Specific IgE with ELISA	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dpter)	Single allergen Dust mite (Dpter)	Clinic
	Hui, 2014 ³⁰ Asia	SCIT Desensitization vaccine**	Asthma diagnosis per Breathing Group of Pediatric Academy; Chinese Medical Association Mild persistent Control status NS	SPT and IgE SPT "positive" and/or allergen-specific IgE in serum (>0.35kUA/l)	Monosensitized Dust mite (DPter)	Single allergen Dust mite (Dpter)	Not specified
	Dreborg, 1986 ²⁹ Europe	SCIT Placebo	Asthma diagnosis GINA criteria Severity Mild to moderate Control status – Controlled (stable dose of ICS)	SPT and IgE SPT 2 + IgE RAST class 1 or greater	Monosensitized Cladosporium	Single allergen Cladosporium	Clinic
	Roberts, 2006 ³⁹ Europe	SCIT Placebo	Asthma diagnosis criteria NR Severity Mild persistent moderate persistent and severe persistent Control status NS	SPT and IgE wheal >3mm IgE NS	Monosensitized Grass (Phleum pratense)	Single allergen Grass (Phleum pratense)	Clinic
	Valovirta, 1984 ²¹ Valovirta, 2006 ²² US	SCIT Placebo	Asthma diagnosis criteria-NS Severity NS Control status NS	SPT and IgE SPT +3 IgE class 2	Polysensitized Birch, Timothy, Cladosporium, HDM, cat	Single allergen Dog	Clinic
	Arroabarren, 2015 ³¹ Europe	SCIT SCIT (3 vs 5 y)	GINA criteria Mild persistent and moderate persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far) And Polysensitized (latex, food, tree, grass, weed, mold, cat, dog)	Single allergen Dust mite (Dpter)	Clinic
Children	Alzakar, 2010 ³⁴ Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA and EPR Excluded severe asthma Control status NS	SPT and IgE Wheal > 3mm; Allergen specific IgE of 0.35 EU/mL	Polysensitized Alternaria, Cladosporium, Penicillium, grass mix, feather mixture, dog, horse, cat, Aspergillus, Fagacae, Betulaceae, plantain, Bermuda grass, Chenopodium, mugwort, Oleaceae and dust mite (Dpter-D far)	Multiple allergens	Clinic
	Tsai, 2010 ³⁵ Asia	SCIT Pharmacotherapy	Asthma diagnosis criteria GINA Severity moderate and severe persistent Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Adkinson, 1997 ³² US	SCIT Placebo	Physician diagnosis asthma Moderate to severe asthma	SPT and IgE	Polysensitized Dust mite (Dpter -Dfar) Trees (white oak) Weeds (ragweed, English plantain), Grass (Grass mix, Bermuda grass) Molds (Alternaria, aspergillus, cladosporium)	Multiple allergens	Clinic

SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

* Authors did not report sensitization status

** the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table A.2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (Range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	64	SCIT Placebo	23.5 (9.3) 23.8 (7.7)	47/53 38/62	32/5 32/5	NR
	Bousquet, 1985 ³	215	SCIT (Rush) Placebo	24 +/- 13(Range 3-72) 24 +/- 11(Range 3-72)	Entire study 68.0/32.0	125/NR 25/NR	12 9.8
	Ameal, 2005 ⁴	63	SCIT Placebo	NR	NR	32/3 31/5	NR
	Vidal, 2011 ⁵	45	SCIT Placebo	25.9 28.3	57/43 58/42	21/2 24/1	NR
	Kohno, 1998 ⁷	16	SCIT Placebo	25.8 26.3	75/25 66/34	8/0 6/2	NR
	Garcia-Ortega, 1993 ¹²	36	SCIT Pharmacotherapy	Range 13-45 Range 13-45	Entire study N 16/20	18/NR 18/NR	NR
	Chakraborty, 2006 ⁸	14	SCIT Placebo	32.22 32.59	NR	8/0 6/0	NR
	Creticos, 1996 ⁹	90	SCIT Placebo	36 +/- 10 35 +/- 10	51/49 50/50	37/8 53/16	At least 1
	Ohman, 1984 ¹⁰	17	SCIT Placebo	26 (Range 22-31) 30 (Range 24-48)	NR NR	9/0 8/0	NR
	Van Metre, 1988 ¹¹	22	SCIT Placebo	Range 21-52 Range 21-52	N 5/6 N 5/6	11/1 11/0	NR
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴	54	HDM SCIT Placebo	29.8 (10.7) 28.5 (7.1)	42/58 39/61	26/6 28/6	14.8 14.1
Mixed age	Casanovas, 2005 ³⁷	23	SCIT Unmodified SCIT Modified	28 34	50/50 45/54	12/NR 11/NR	2
	Ibero, 2006 ¹⁷	30	SCIT Placebo	Median: 10 Range: 8-15 Median: 12 Range: 8-16	Entire study 63/47	15/NR 15/2	NR
	Lozano, 2014 ²⁶	43	SCIT Combination	Median: 9 Range: 6-12 Median: 9 Range: 6-14	48/52 55/45	21/1 20/2	1

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (Range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
	Baris, 2014 ²⁴	55	SCIT + Vit D SCIT Pharmacotherapy	9.2 (2.6) 8.8 (1.1) 7.9 (2.6)	29/81 47/53 50/50	17/1 15/2 18/2	NR
	Zielen, 2010 ²⁷	66	SCIT + ICS ICS alone	Median: 9 Range: 6-17 Median: 11 Range: 6-16	66/34 69/31	33 32	Median: 3 Median: 2
	Altintas, 1999 ¹⁹	35	Adsorbed Aluminum Hydroxide IT Adsorbed Calcium Phosphate SCIT Aqueous SCIT Placebo	10.8 +/- 3.7 10.0 +/- 3.7 11 +/- 4 11 +/- 3	80/20 60/40 55/45 60/40	10/ NR 10/ NR 9/ NR 5/ NR	NR
	Schubert 2009 ³⁸	34	SCIT Cluster SCIT Classic	10 8.5	NR NR	20/2 14/2	NR
	Hui, 2014 ³⁰	90	SCIT Desensitization vaccine*	10.1 (2.2) 9.8 (1.5)	53/47 49/51	45/5 45/4	3.5 3.4
	Dreborg, 1986 ²⁹	30	SCIT Placebo	11 (Range 5-17) 11 (Range 5-17)	NR	16/NR 14/NR	NR
	Roberts, 2006 ³⁹	37	SCIT Placebo	9.2 (4.4) 10.6 (2.9)	72/28 81/29	18/4 17/4	NR
	Valovirta, 1984 ²¹ Valovirta, 2006 ²²	27	SCIT Placebo	11 (Range 5-18) 10.5 (Range 5-16)	60/40 58/42	15/0 12/0	NR
	Arroabarren, 2015 ³¹	63	5-year IT 3-year IT	9.26 (NR) 8.9 (NR)	NR	36/NR 27/NR	NR
Children	Alzakar, 2010 ³⁴	242	SCIT Pharmacotherapy	9.8 (1.7) 10 (1.5)	55/45 60/40	105 137	NR
	Tsai, 2010 ³⁵	40	SCIT Pharmacotherapy	8.6 (2.99) 8.35 (2.43)	70/30 35/65	20/0 20/0	NR

SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified * the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table A.3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	SCIT Placebo	Conventional and rescue therapy	12 administrations of 0.5mL/vial 2 were administered in monthly intervals	NR	Monthly	20.35 µg Der p 1 and 12.30 mg Der p 2 per mg	54 weeks
	Bousquet 1985 ³	SCIT rush Placebo	NR	3000 BU (=to 0.1 ml of 1/100 w/v)	NR	Weekly	NR	7 weeks (not clearly stated)
	Ameal, 2005 ⁴	SCIT Placebo	Only rescue (B2)	0.5 mL of 70 µg/mL	NR	Monthly	14.25 µg of Der p 1/ml and 8.61 of Der p 2	12 months
	Vidal, 2011 ⁵	SCIT Placebo	Both NS	0.8ml	NR	Monthly	4.8 µg DP1, 3.2 µg DP2	4 months

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Kohno, 1998 ⁷	SCIT rush Bronchodilators	Conventional therapy	0.15-0.30 ml of 1/10 wt/vol	NR	Weekly for 2 months then every 2 weeks for 6 months	1 mg dust mite extract = 9.8 ng of major allergens Der1 and Der2 (5.4 ng was D far)	6 months
	Garcia-Ortega, 1993 ¹²	SCIT dust mite cluster Pharmacotherapy	Conventional therapy (bronchodilators/ usual care)	100000 SQ	2000000 SQ	Every 15 days	NR	7 months
	Chakraborty, 2006 ⁸	SCIT Placebo	NR	1:2500 wt/vol	NR	Conventional Weekly	0.5 µg	2 years
	Creticos, 1996 ⁹	SCIT Ragweed Placebo	Only rescue medication	0.5 mL of 1:10 dilution (actual mean dose in year = 4 µg of Amb a1)	NR	Every 2 weeks for 3 months thereafter every 4 weeks	10 µg of Amb a1	2 years
	Ohman, 1984 ¹⁰	SCIT Cat Placebo	NR	0.3 ml of extract containing 13 units of cat allergen 1 per ml or 300 µg/ml of cat albumin)	10.9 units' cat allergen or 272 µg of cat albumin	Weekly	13 units of cat allergen 1 U/ml or 300 µg /ml of cat albumin)	16 weeks
	Van Metre, 1988 ¹¹	SCIT Cat Placebo	Conventional therapy	1.0 mL of 4 .56 FDA units of Fel d 1 per mL.	NR	Biweekly	4 .56 FDA units of Fel d 1	At least 1 year
	Blumberga, 2011 ¹³ Blumberga, 2006 ¹⁴	HDM SCIT Placebo	Conventional and rescue therapy	100,000 SQ	20	6 weeks	NR	3 years
	Casanovas, 2005 ³⁷	SCIT modified vs SCIT unmodified	NR	Target: 154 µg Actual: 154 µg	Target: 615.69 µg Actual: 615.69 µg	NR	Max concentration 308.50 µg/mL or 2464.90 Max concentration 2400 µg/mL or 24696 PNU/mL	11 weeks
Mixed age	Ibero, 2006 ¹⁷	SCIT Placebo	Conventional therapy and rescue medication	Target: 42.5 µg Actual: 42.5 µg	216.75 µg	Monthly	NR	4 months
	Lozano, 2014 ²⁶	SCIT Pharmacotherapy	Both (LTRA, LABA, ICS)	10,000 AUeq	NR	Monthly	4 µg Der p1, 15 µg Der p2	8 months
	Baris, 2014 ²⁴	SCIT + Vit D SCIT alone Pharmacotherapy	Both	NR	NR	Buildup NS Maintenance monthly	NR	12 months
	Zielen, 2010 ²⁷	SCIT Pharmacotherapy (ICS alone)	Both (ICS)	0.6 mL of strength B= 10,000 TU/ml	NR	6 weeks	7 ug Der p 1 6 ug Der p 2	2 years

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Altintas, 1999 ¹⁹	SCIT Dust mite Absorbed Aluminum SCIT Dust mite Absorbed calcium	NR	50000 -100000 SQ (targeted) 60000 to 100000 SQ (actual) 6 -10 IR (10 IR ≡ 1/1000w/v)	NR	Every 4 weeks	NR	2 years
	Schubert, 2009 ³⁸	SCIT dust mite cluster alum-precipitated SCIT dust mite conventional alum-precipitated	Conventional therapy	5000 TU after 6 weeks 5000 TU after 14 weeks	Either 30,825 TU or 33,825 TU 21, 325 TU	Every 2-4 weeks Every 2 weeks	NR	16 weeks
	Hui, 2014 ³⁰	SCIT Desensitization vaccine*	Both (NS)	100,000 U/ml	1,025,000 U/ml	Every 4-6 weeks	NR	51 weeks
	Dreborg, 1986 ²⁹	SCIT Cladosporium Placebo	Conventional therapy	100000 BU (reached after 18 weeks)	NR	Every 4 weeks	NR	10 months
	Roberts, 2006 ³⁹	SCIT Cladosporium Placebo	Conventional therapy and rescue therapy	Target: 100,000 SQ-U. Actual: 100,000 SQ-U.	NR	Every 6 weeks (+/- 2 weeks)	20	2 years
	Valovirta, 1984 ²¹ Valovirta, 2006 ²²	SCIT Dog alum-precipitated Placebo	NR	100,000 SQ U (Range from 8000 to 50000 in 4/15 subjects)	NR	6 weeks	NR	1 year
	Arroabarren, 2015 ³¹	SCIT 3 years SCIT 5 years	Both (NS)	Mix of conventional and cluster	NR	Monthly	3.6 µg Der P1 per dose	3 years vs 5 years
Children	Alzakar, 2010 ³⁴	SCIT Pharmacotherapy	Conventional therapy (beclomethasone + aminophylline as part of study)	0.5 of stock standardized extracts	NR	Every 15 days then every 4-6 weeks	NR	12 months
	Tsai, 2010 ³⁵	SCIT Pharmacotherapy	Both (NS)	NS	initial dose of 0.5 AU/mL weekly and increased 25-100% weekly until optimal maintenance dose reached	Biweekly	Dpter and Dfar (10,000 AU/mL)	3 months

NR: Not reported

BU: Biological units

SQU: standard quality units

PNU: Protein Nitrogen Unit

AU Allergy unit

µg: microgram

Ag/ml: major protein unit

TU: Treatment units

wt/vol Weight to volume

SE: Specific units of short-term immunotherapy

LTRA: Leukotriene receptor antagonist

LABA: Long acting Beta agonist

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table A.4 - Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Zielen, 2010 ²⁷	Dust mite NS	SCIT + ICS ICS alone	33 32	No anaphylaxis occurred during the study	0	0	NA
Bousquet 1985 ³	Dust mite NS	SCIT rush Placebo	20 10	3 systemic reactions not specified, treated with Epinephrine*	3 0	NR	0.15
Baris, 2014 ²⁴	Dust mite Mild and moderate asthma	SCIT + Vit D SCIT alone Pharmacotherapy	17 15 18	Systemic reaction not specified, treated with epinephrine*	0 1 0	NR	0.03
Casanovas, 2005 ³⁷	Grass Mild and moderate asthma	SCIT modified vs SCIT unmodified	11 12	Urticaria, conjunctivitis, and bronchospasm treated with epinephrine*	0 1	NR	NA
Creticos, 1996 ⁹	Ragweed Moderate to severe asthma	SCIT Placebo	37 40	Bronchospasm and hypotension requiring epinephrine (was in the placebo group but received immunotherapy by mistake)*	0 1	NR	NA

*Not defined as anaphylaxis but symptoms and treatment are consistent with anaphylaxis

Table A.5 - Hypersensitivity

No study reported on hypersensitivity

Table A.6 – Local Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	Dust mite Mild and Moderate asthma	SCIT Placebo	32 32	erythema <5cm	2 2	NR NR	0
Ameal, 2005 ⁴	Dust mite Mild and Moderate asthma	SCIT Placebo	29 26	cutaneous (wheal)	2 3	NR NR	-0.046
Vidal, 2011 ⁵	Dust mite Mild and Moderate asthma	SCIT Placebo	21 24	Not specified	3 (14.3%) 3 (12.5%)	10 4	0.018
Ohman, 1984 ¹⁰	Cat Severity NS	SCIT Placebo	9 8	2 patients/3 reactions: Large local reaction required modifications of the immunotherapy schedule classified as severe	2 (22%) 0	No.317 to 0,4R	0.222
Van Metre, 1988 ¹¹	Cat Severity NS	SCIT Placebo	11 (336 injections)	local reactions: Induration > 5 cm Reactions reported during first year of IT – no reactions reported for placebo arm	Reaction rate (7.7 reactions/100 injections)	26	NA

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Casanovas, 2005 ³⁷	Timothy Grass Mild and Moderate asthma	SCIT unmodified SCIT modified	12 11	Immediate local reactions	NR NR	3 6	NA
				Delayed local reactions	NR NR	18 12	NA
Lozano, 2014 ²⁶	Dust mite Intermittent, Mild and Moderate asthma	SCIT Pharmacotherapy	21 20	Local AEs requiring dose modification	0 0	NR NR	0
Baris, 2014 ²⁴	Dust mite Mild and Moderate asthma	SCIT + vitamin D SCIT alone Pharmacotherapy	17 15 18	Local urticarial plaques at their injection sites	6 7 0	NR NR NR	0.013
Ibero, 2006 ¹⁷	Dust mite Mild and Moderate asthma	SCIT Placebo	15 13	Pain and heat over a 24-hour period after the first 2 injections	1 0	1 0	0.067
				Pain immediately after the second maintenance dose	1 0	1 0	0.067
				Induration (1 cm in diameter) and pruritus after the third maintenance dose	1 0	1 0	0.067
Zielen, 2010 ²⁷	Dust mite Severity NS	SCIT + ICS ICS alone	33 32	most frequent symptoms were application site itching and application site paresthesia	11 (33.3%) 0	NR NR	0.333
Schubert 2009 ³⁸	Dust mite Mild and Moderate asthma	cluster schedule classic schedule	20 (341 injections) 10 (151 injections)	Local events classified as mild Redness: 97 (28%), Swelling <5cm: 57 (16%), Swelling > 5cm: 22 (6%), painful swelling >3h: 8 (2%) Redness: 40 (26%), Swelling <5cm: 20 (13%), Swelling > 5cm: 17 (11%), painful swelling >3h: 3 (2%)	events per patient 9.25 8	185 (54%) 80 (53%)	NA SCIT vs SCIT
Dreborg, 1986 ²⁹	Cladosporium Mild and Moderate asthma	SCIT vs Placebo	16 14	Urticaria	18% 0	NR	0.011
Roberts, 2006 ³⁹	Grass Mild, Moderate and Severe asthma	SCIT Placebo	18 17	Episodes of pruritus, pain, or swelling	NR NR	13 11	NA
Hui, 2014 ³⁰	Dust mite Mild and Moderate asthma	SCIT Desensitization vaccine*	45 45	local induration, induced cough and urticaria	NR	202/ 1735 (11.7%) injections	NA
Tsai, 2010 ³⁵	Dust mite Moderate and Severe asthma	SCIT Pharmacotherapy	20 20	Local red swelling at injection site	8 0	NR NR	0.4
Valovirta, 1984 ²¹ Valovirta, 2006 ²²	Dog Severity NS	SCIT Placebo	15 12	309: 227<1cm, 71 1-3cm, 11>3cm 251: 163<1cm, 82 1-3cm, 6>3cm	309 251	events per patient 20 21	-0.317

NR: Not reported

* the control group received

standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table A.7 – Systemic Reactions

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Garcia-Robaina, 2006 ¹ Gallego, 2010 ²	Dust mite Mild and Moderate asthma	SCIT Placebo	32 32	54 weeks	Not specified	Hoarseness	0 0	NR NR	0
Bousquet, 1985 ³	Dust mite Severity NS	SCIT (Rush) Placebo	20 10	7 weeks	Not specified	4/20 developed a “systemic reaction” (unspecified) No reactions in control group	4 (20%) 0	NR	0.2
Ameal, 2005 ⁴	Dust mite Mild and Moderate asthma	SCIT Placebo	29 26	12 months	Not specified	Pruritus (1 pt) Urticaria (1 pt) Note: occurred 12 hours later in patient known to have urticaria “Delayed mild reaction” (3 pts) Note: control reactions NS	5 3	NR	0.057
Vidal, 2011 ⁵	Dust mite Mild and Moderate asthma	SCIT Placebo	21 24	4 months	Not specified	“Mild-Moderate reaction” in 1 event “unlikely related to SCIT” (7 events) 1 probable reaction (5 unlikely)	6 (28.6%) 5 (11.1%)	8 6	0.077
Kohno, 1998 ⁷	Dust mite Severity NS	SCIT Placebo	8 6	6 months	Not specified	2 patients dropped out of the study due to respiratory infection	2 0	NR	0.25
Chakraborty, 2006 ⁸	Grass Severity NS	SCIT Placebo	8 6	2 years	Not specified	Respiratory AE	0 0	NR NR	0
Creticos, 1996 ⁹	Ragweed Moderate and Severe asthma	SCIT Placebo	37 40	2 years	Not specified	5 events “mild reactions that resolved spontaneously”	NR NR	NR NR	NA
						9 events systemic reactions: rhinitis, urticaria, angioedema (or combination of these): required antihistamines or epinephrine	7 1	14 1	0.164
						1 patient Bronchospasm + hypotension (Allergen given by mistake)	2 0	NR	0.054

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Ohman, 1984 ¹⁰	Cat Severity NS	SCIT Placebo	9 8	16 weeks	Not specified	Rhinoconjunctivitis, asthma, itching, facial swelling and hives. "all were mild and responded promptly to treatment" Note: skin test titer, bronchial reactivity, and sensitivity of white blood cells to allergen did not predict reliably those subjects who would have reactions to immunotherapy	4 (44%) 1 (12.5%)	10 2	0.319
Garcia-Ortega, 1993 ¹²	Dust mite Severity NS	SCIT (cluster) Pharmacotherapy (bronchodilators/ usual care)	18 18	7 months	Not specified	Mild reactions: 2 wheezing classified as moderate 1 generalized urticaria (classified as moderate)	3 (16%) 0	NR NR	0.167
						Generalized urticaria classified as moderate	5% 0	NR	0.028
Casanovas, 2005 ³⁷	Timothy Grass Mild and Moderate asthma	SCIT unmodified SCIT modified	12 11	11 injections total	Highest maintenance dose	Immediate reactions: Group A 1 Perioral itching 1 Nasal-ocular symptoms, dyspnea, dizziness, cough 1 Urticaria, rhinoconjunctivitis, bronchospasm Group B 1 Palatal itching	NR	4 (114 injections) 1 (121 injections)	0.027 (Calculated for events per injections)
						Delayed systemic reactions: Group A 1 "unspecified symptoms" 1 Naso-ocular symptoms, abdominal pain, diarrhea, headache 1 Rhinoconjunctivitis 1 Urticaria, headaches, pharyngeal discomfort Group B: 1 headache and nasal obstruction	NR	8 (114 injections) 1 (121 injections)	0.062 (Calculated for events per injections)
Lozano, 2014 ²⁶	Dust mite Intermittent, Mild and Moderate asthma	SCIT Pharmacotherapy	21 20	8 months	Not specified	Systemic AEs requiring dose modification	0 0	NR	0

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Baris, 2014 ²⁴	Dust mite Mild and Moderate asthma	SCIT + vitamin D SCIT alone Pharmacotherapy	17 15 18	12 months	Not specified	2 mild asthma 1 "systemic reaction" within 20 minutes after injection of vial 4, requiring Epinephrine	2 1 0	NR NR NR	0.093
Ibero, 2006 ¹⁷	Dust mite Mild and Moderate asthma	SLIT aqueous Placebo	15 13	4 months	After 2 nd or 3 rd dose	1 mild rhinitis and asthma 1 mild dyspnea No meds were needed to treat any of the reactions	2 0	2 0	0.133
Zielen, 2010 ²⁷	Dust mite Severity NS	SCIT + ICS ICS alone	33 32	2 years	Not specified	Cough, rhinitis	2 (6.1%) 0	NR	0.061
Schubert 2009 ³⁸	Dust mite Mild and Moderate asthma	cluster schedule classic schedule	20 (341 injections) 10 (151 injections)	16 weeks	Not specified	Reactions classified as mild 12 reactions: 10 cough-2 dyspnea 7 reactions: 6 cough-1 dyspnea	0.7 events per patient 0.8 events per patient	12 reactions (3.5% of injections) 7 reactions (4.6% of injections)	NA SCIT vs SCIT
						Bronchial asthma - classified as moderate	0.3 events per patient 0.2 events per patient	2 reactions (0.6% of injections) 1 reaction (0.7% of injections)	NA SCIT vs SCIT
Roberts, 2006 ³⁹	Grass Mild, Moderate and Severe asthma	SCIT Placebo	18 17	2 years	Not specified	pulmonary reactions that responded to bronchodilators	4 3	4 3	0.046
						Others: Eczema, urticaria, rhinoconjunctivitis	NR	21 9	NA
Hui, 2014 ³⁰	Dust mite Mild and Moderate asthma	SCIT desensitization vaccine *	45 45	51 weeks	During dose increasing phase	NS and not divided by group	NR	1/ 1735 injections (0.05 %)	NA
Alzakar, 2010 ³⁴	Dust mite, Grass, Mold, pets, and Trees Excluded severe asthma	SCIT Pharmacotherapy Becлометазон + Аминофиллин	85 112	12 months	Not specified	1 "mild respiratory involvement" 8 "skin rash" Did not specify if these are treatment or control groups	9 (11%)	NR	NA
Arroabarren, 2015 ³¹	Dust mite Mild and Moderate asthma	5-year IT 3-year IT	36 NR	3 or 5 years	Not specified	2 subjects with asthma had an asthma episode within 30 minutes of maintenance dose, treated with bronchodilators	2 (2.46%) NR	0.03% of doses	NA
Tsai, 2010 ³⁵	Dust mite Moderate and Severe asthma	SCIT pharmacotherapy	20 20	3 months	Not specified	Not specified	0 0	NR	0

Study	Allergen and Asthma Severity	Arms	N	Duration of SCIT Treatment	Time During SCIT When Reaction Occurred	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (For AEs reported as patients)
Adkinson, 1997 ³²	Multiple Moderate to severe asthma	SCIT Placebo	61 60	30 months	Not specified	114 total systemic reactions (52 treated with adrenergic drugs and all responded to treatment)	21 (34%) 4 (7%)	2.6/100 injections	0.278

* the control group received standardized glucocorticoid management and a desensitization vaccine(details not provided)

Table A.8 – Deaths*

No deaths reported

*Data abstracted ONLY if studies specifically reported on deaths

SECTION B SCIT SAFETY FOR NON RCTs

Table B.1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Quiralte, 2013 ⁴⁰ Europe	SCIT cluster SCIT conventional	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Clinic
	Rank, 2008 ⁴¹ US	SCIT Cluster wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE wheal >3mm IgE NS	Both mono and polysensitized Not specified	Multiple allergens	Not specified
	Rank, 2014 ⁴² US	SCIT wo comparator	Asthma diagnosis not described Severity NS Asthma control NS	Not reported	Not reported	Multiple allergens	Clinic
	Sana, 2013 ⁴³ Europe	SCIT wo comparator	Asthma diagnosis criteria NR Severity Moderate persistent Control status NS	SPT and IgE NS	Not reported	Multiple allergen (Alustal – respiratory allergens)	Not specified AE treated in ICU
	Kim, 2011 ⁴⁴ Asia	SCIT Rush and ultrarush wo comparator	Asthma diagnosis Pulmonary tests (20% decrease in FEV1 following < 8mg ethacholine/mL or reversibility of FEV1 > 15% after bronchodilator + clinical symptoms) Severity NS Control status NS	SPT and IgE Wheal ≥3 mm above negative control; serum-specific IgE antibody tests to HDM ($\geq 0.7 \text{ kU/L}$)	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Sanchez-Morillas, 2005 ⁴⁶ Europe	SCIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE SPT NS IgE: Cupressus arizónica 0.94 KU/l, Cupressus sempervirens 1.26 KU/l	Monosensitized Tree cypress	Single allergen Tree Arizona cypress	Clinic
	Ozden, 2009 ⁴⁷	SCIT wo comparator	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Single allergen Timothy Grass	Clinic
Mixed age	Gozde Kanmaz, 2011 ⁴⁸ US	SCIT VS. SCIT	Asthma diagnosis GINA criteria Severity Mild persistent and moderate persistent Control status NS	SPT > 3mm	Monosensitized Dust mite (Dpter OR D far)	Single allergen Dust mite (Dpter-D far)	Not reported
	Kartal, 2015 ⁴⁵ Europe	SCIT wo comparator	Asthma diagnosis not described Severity NS Asthma control NS	Not described	Polysensitized Dust mites (HDM), Pollen,cat, mold	Single allergen Dust mite (HDM)	Clinic
	Copenhaver, 2011 ⁴⁹ US	SCIT Cluster wo comparator	Asthma diagnosis Physician Severity NS Control status NS	Not reported	Not reported	Multiple allergens Dust mites, grass, trees, cat, dog, mold, cockroach	Clinic
	Confino-Cohen, 2010 ⁵⁰ Asia	SCIT wo comparator	Asthma diagnosis NS Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Clinic
	Smits, 2007 ⁵¹ US	SCIT Rush wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT NS	Polysensitized grass, dust mites, cats, ragweed	Multiple allergens	Clinic
	Chen, 2014 ⁵² Asia	SCIT adults SCIT children	Asthma diagnosis NS Severity NS Control status NS	SPT and IgE SPT NS IgE Class II	Monosensitized and Polysensitized	Dust mite (Dpter)	Clinic
	Cardona, 2014 ⁵³ South America	SCIT Ultrarush wo comparator	Asthma diagnosis NR Severity NS Control status NS	Not reported	Monosensitized Dust mite (Dpter)	Dust mite (Dpter)	Clinic
	Santos, 2015 ⁵⁴ Europe	SCIT wo comparator	Asthma diagnosis not described Severity NS Asthma control NS	Not reported	Not reported	Pollen, dust mites (NS)	Clinic
	Eng, 2006 ⁵⁵ Europe	SCIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE NS	Monosensitized Grass	Single allergen Grass	Not specified

SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

* Authors did not report sensitization status

Table B.2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (range)	Sex (% male/female)	Patients Enrolled/ Dropouts	Duration of disease (Mean years affected)
Adults	Quiralte,2013 ⁴⁰	183 169	Cluster-SCIT Short Conventional-SCIT	26.2 (13.3) 26.7 (13.8)	49%/51% 57.4%/42.6%	19/NR 26/NR	NR
	Rank, 2008 ⁴¹	NA	Systemic Reaction with SCIT No Systemic Reaction with SCIT	NR	NR	NR	NR
	Rank, 2014 ⁴²	1	Case Report	42 years' old	NA/1	1/NR	NR
	Sana, 2013 ⁴³	1	Case Report	17 years' old	NA/1	1/NR	NR
	Kim, 2011 ⁴⁴	NR	BA rush IT	25.5 (10.3)	27.8%/NR	18/NR	NR
	Sanchez-Morillas, 2005 ⁴⁶	1	Case Study	66 years' old	NA/1	1/NR	3 years
	Ozden, 2009 ⁴⁷	1	Case Study	NR	NR	1/NR	NR
Mixed age	Gozde Kanmaz, 2011 ⁴⁸	102	SCIT Pharmacotherapy	12.4 (2.3) 12.5 (2.4)	46/54 65/35	50/NR 52/NR	NR
	Kartal, 2015 ⁴⁵	706	SCIT wo comparator	25.7 (12.2)	54.7%/45.3%	1816/NR	NR
	Copenhaver, 2011 ⁴⁹	NR	SCIT wo comparator	NR	NR	NR	NR
	Confino-Cohen, 2010 ⁵⁰	133	SCIT wo comparator	NR	NR	NR	NR
	Smits, 2007 ⁵¹	505	SCIT wo comparator	NR	NR	NR	NR
	Chen, 2014 ⁵²	130	SCIT – Children SCIT - Adults	9.62 (2.71) 28.31 (10.3)	62.45%/NR 47.9%/NR	67/16 63/31	NR
	Cardona, 2014 ⁵³	313	SCIT wo comparator	15 (NR)	NR/51%	313/NR	NR
	Santos, 2015 ⁵⁴	NR	SCIT wo comparator	NR	NR	NR/NR	NR
	Eng, 2006 ⁵⁵	NR	SCIT No SCIT	23.8 (NR) 23.4 (NR)	9/3 7/3	NR/NR	NR

Table B.3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Quiralte,2013 ⁴⁰	SCIT Cluster SCIT Conventional	NR	NR	Targeted: 14.8 IR Actual: 8 IR Targeted: 16.5 IR Actual: 8 IR	Weekly	NR	4 weeks or 8 weeks
	Rank, 2008 ⁴¹	Systemic Reaction with SCIT	Conventional therapy and	NR	NR	NR	NR	NR

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
		No Systemic Reaction with SCIT	Rescue therapy					
	Rank, 2014 ⁴²	Case Study	NR	NR	Targeted: NR Actual: .25	Cluster	NR	NR
	Sana, 2013 ⁴³	Case Study	NR	NR	NR	NR	NR	NA
	Kim, 2011 ⁴⁴	Rush IT	Conventional therapy and Rescue therapy	Targeted: 0.8 mL of the highest allergen concentration (5000 units/ml) once a month as maintenance therapy Actual: NR	Targeted: 5,000 units/ ml Actual: NR	Monthly	NR	3 days
	Sanchez-Morillas, 2005 ⁴⁶	Case Study	NR	Targeted: NR Actual: Depot preparation monthly for 2 years	Targeted: NR Actual: 19475 STU accumulated	Monthly	NR	2 years
	Ozden, 2009 ⁴⁷	Case Study	NR	NR	NR	NR	NR	NR
Mixed age	Gozde Kanmaz, 2011 ⁴⁸	SCIT Pharmacotherapy	NR	Targeted: NR Actual: 100,000 SQ-U Targeted: NR Actual: 0.00001, 0.0001, 0.001 and 0.01 mg/ml	NR	Weekly	NR	33 months average
	Kartal, 2015 ⁴⁵	SCIT wo comparator	NR	Targeted: NR Actual: 0.8 ml/5000 TU/ml (NH) and 0.8 ml/10 IR/ml (P)	Targeted: NR Actual: 10 IR/ml	Weekly	NR	30 years
	Copenhaver, 2011 ⁴⁹	SCIT wo comparator	NR	NR	Targeted: concentration 1:1, 0.5ml Actual: NR	Cluster	NR	8 office visits
	Confino-Cohen, 2010 ⁵⁰	SCIT wo comparator	Conventional therapy and Rescue therapy	NR	NR	NR	NR	NR
	Smits, 2007 ⁵¹	SCIT wo comparator	NR	Targeted: 0.4ml Actual: 0.4ml	NR	Every 4-10 days	NR	3 days
	Chen, 2014 ⁵²	SCIT – Children SCIT - Adults	NR	Targeted: 100,000 SQ-U/mL Actual: NR	NR	Every 6 weeks	NR	NR
	Cardona, 2014 ⁵³	SCIT wo comparator	NR	Targeted: 0.5 ml 50 DPP Actual: 0.5 ml 50 DPP	NR	Monthly	NR	NR
	Santos, 2015 ⁵⁴	SCIT wo comparator	NR	NR	NR	NR	NR	NR
	Eng, 2006 ⁵⁵	SCIT No SCIT	Conventional therapy and	NR	NR	NR	NR	2 years

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
			Rescue therapy					

Table B.4 – Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Comparative Value
Quiralte, 2013 ⁴⁰	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	No anaphylaxis events were reported	0	0
Confino-Cohen, 2010 ⁵⁰	Multiple allergens Severity NS	SCIT wo comparator	133 (21,022 injections)	Frequency of anaphylaxis in a case series of SCIT in children and adults. Anaphylaxis was classified as "mild, moderate, or severe" based on symptoms. Reactions were classified as Uniphasic or Biphasic. Uniphasic reactions: 54 out of 101 patients had asthma Biphasic reactions: 9 out of 11 patients had asthma	54/101 (54) 9/11 (82) Incidence 1.3%	P=0.07
Rank, 2014 ⁴²	Grass Severity NS	SCIT wo comparator	1	flushing, nasal congestion, nasal itching, and chest tightness with wheezing; treated with epinephrine IM, diphenhydramine IM, prednisone, and albuterol note: patient was receiving cluster SCIT during the pollen season	1	1

Table B.5 - Hypersensitivity

No study reported on hypersensitivity

Table B.6 – Local Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Quiralte, 2013 ⁴⁰	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	Local urticarial plaques at their injection sites	85 (25.1%) 87 (27.3%)	177 (6.5% of doses) 274 (10.7% of doses)
Kartal, 2015 ⁴⁵	Dust mite Severity NS	SCIT W/O COMP	1816	Large local reaction	93	NR
				Small local reaction	71	NR
Ozden, 2009 ⁴⁷	Timothy Grass Severity NS	SCIT W/O COMP	1	multiple subcutaneous itchy nodules on the lateral aspects of both arms, at the site of previous immunotherapy injections	1	Case report

Table B.7 – Systemic Reactions

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Gozde Kanmaz, 2011 ⁴⁸	Grass and Dust mite Mild and Moderate asthma	SCIT Pharmacotherapy	50 52	Worsening of condition attributed to mild systemic reaction	1 0	NR
				Undercurrent illnesses, or worsening of condition	5 0	NR
Quiralte, 2013 ⁴⁰	Dust mite, Mold, Animals, Trees and Grass Severity NS	SCIT cluster SCIT conventional	339 (2712 doses) 319 (2552 doses)	Total Systemic reactions	5 (1.5 %) 14 (4.4 %)	5 (0.2% of doses) 24 (0.9 %of doses)
				Systemic reactions Grade 0 = “Non-specific systemic symptoms”	1 (0.3 %) 8 (2.5 %)	1 13
				Systemic reactions Grade 1 = localized urticaria, rhinitis or mild asthma; peak flow [PEF] <20% decrease from baseline)	3 (0.9 %) 4 (1.2 %)	3 8
				Systemic reactions Grade 2 = generalized urticaria, moderate asthma or both; PEF <40% decrease from baseline	1 (0.3 %) 2 (0.6 %)	1 3
Rank, 2014 ⁴²	Grass Severity NS	SCIT wo comparator	1	flushing, nasal congestion, nasal itching, and chest tightness with wheezing; treated with epinephrine IM, diphenhydramine IM, prednisone, and albuterol note: patient was receiving cluster SCIT during the pollen season	1	1
				Odds of an SR to SCIT for a patient with asthma were lower than those without. Patients with asthma with SR 1 (3%) Patients with asthma without SR 1144 (11%) OR 0.29 (0.04–2.14)	NR	NR
Kim, 2011 ⁴⁴	Dust mite Severity NS	SCIT wo comparator	18	1 participant had moderate bronchospasm (grade 2). Occurred at therapeutic dose 4000 (planned max therapeutic dose = 4000). Onset time 160 min. Treatment: Inhalation of 200 µg of salbutamol.	1	NR
				1 participant had localized urticaria grade 1 systemic reaction. Planned max therapeutic dose = 4000units. Allergen dose that induced SR = 4000 TU Onset time = 30 min	1	NR
				2 had generalized urticaria(grade 2). Occurred at therapeutic dose 4000 (planned max therapeutic dose = 4000). Onset time 160 min. Treatment: Inhalation of 200 µg of salbutamol.	2	NR

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Kartal, 2015 ⁴⁵	Dust mite Severity NS	SCIT wo comparator	702	Only results available regarding asthma patients: The rate of systemic reactions in asthma plus AR patients (11%) was higher than asthma alone (1.5%) and AR alone patients (9.5%). The risk of SR was lowest for asthmatic patients than in patients with asthma plus rhinitis (OR, 0.13; 95% CI, 0.04-0.41; p50.001), or (OR, 0.15; 95% CI, 0.05-0.48; p50.001)		NR
Sanchez-Morillas, 2005 ⁴⁶	Trees Severity NS	SCIT wo comparator	1	Leukocytoclastic Vasculitis on both legs, diagnosed by skin biopsy, after being on depot SCIT for 2 years, the same episodes occurred with the next 2 doses of SCIT	1	1
Copenhaver, 2011 ⁴⁹	Dust mites, Grass, Trees, Cat, Dog, Mold, Cockroach Severity NS	SCIT wo comparator	127	Not specified Significantly higher than patients without asthma (19.7% vs 7.3%, P = .0005)	19.7%	25
Smits, 2007 ⁵¹	Grass, Dust mite, Animals, and Weeds Severity NS	SCIT wo comparator	505	Study included patients with asthma and rhinitis. 14 of the 18 SRs were in patients with asthma (79%)	14	NR
Chen, 2014 ⁵²	Dust mite Severity NS	SCIT children SCIT adults	67 63	Total non-fatal systemic reactions	16 (23.88%) 8 (12.7%)	NR
Cardona, 2014 ⁵³	Dust mite Severity NS	Ultra-rush SCIT wo comparator	313	4 patients had hives and/or wheezing 2 patients had rhinorrhea ocular itching 6 out of 8 patients who had systemic reactions had asthma	6	NR
Santos, 2015 ⁵⁴	Pollen and Dust mites Severity NS	SCIT wo comparator	3732 (22332 injections both asthma and rhinitis)	3 year retrospective study; there were 26 reactions (0.1% of administrations) in 16 (0.6%) of the patients 9 subjects with asthma had systemic effects (not clear what number of subjects had asthma) Most of the grade 2 reactions occurred in individuals with asthma and presented as cough and/or dyspnea and/or asthma exacerbation (79%)	NR	NR

Table B.8 – Deaths*

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Rank, 2008 ⁴¹	Dust mite and Animals Severity NS	SCIT wo comparator	338	There were no fatalities reported	0	0
Kartal, 2015 ⁴⁵	Dust mite Severity NS	SCIT wo comparator	1816	There were no fatalities reported	0	0
Sana, 2013 ⁴³	Alustal – respiratory allergens Moderate asthma	SCIT wo COMP	1	12 hours after initiation of treatment, she complained of abdominal pain, vomiting and diarrhea without fever Two days later, she developed an acute respiratory failure and was	1	1

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
				referred to the intensive care unit on day 4 she developed hypoxic coma leading to intubation and mechanical ventilation. Rapidly, she experienced intractable shock and acute renal impairment. By day 5 she developed multiorgan failure and died		

*Data abstracted ONLY if studies specifically reported on deaths

Appendix F: KQ3- What is the evidence for the efficacy of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

KQ3 – What is the evidence for the efficacy of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- tress- animal-multiple allergen)

Table 1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Virchow, 2016 ⁵⁶ Europe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Moderate to severe Asthma Pulmonary tests (PFT reversibility) Poorly Controlled	SPT and IgE SPT ≥ 3 mm SIgE ≥ 0.70 kU/L	Both mono and polysensitized “Patients could have multiple sensitization but no perennial asthma caused by other allergens”	Single allergen Dust mite (Dpter-D far)	Clinic
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹ Europe	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	Asthma diagnosis GINA criteria (steps 2 and 3) Pulmonary tests (documented history of reversible airway obstruction) Mild persistent and moderate persistent Controlled (ACQ scores and ICS dose of 100 to 800 mg/d)	SPT and IgE wheal size >3mm to D farinae, D pteronyssinus, or both IgE NS	Both mono and polysensitized	Single allergen Dust mite (Dpter-D far)	Not specified
	Maloney, 2016 ⁶⁰ US	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity not specified Controlled (FEV1 ≥70% predicted, no more than 2 symptoms per week, no more than 2 days of SABA use per week, no more than 2 awakenings per month due to asthma)	SPT and IgE wheal diameter ≥5mm larger than saline control; serum-specific IgE ≥ 0.7 kU/L or at least class II (all against D pter or D far)	39 patients monosensitized Dust mite (Dpter-D far) 156 patients polysensitized grass, cat, dog, mold, birch, mugwort	Single allergen Dust mite (Dpter-D far)	Home
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶² Multisite	SLIT (A) Placebo	Pulmonary tests (bronchial reversibility test and methacholine challenge) Mild persistent and moderate persistent	SPT and IgE wheal diameter ≥ 4 mm in an SPT after washout of antihistamines, specific IgE ≥ 0.70 kU/l	Polysensitized Dust mites (Dpter-D far), cat. dog	Single allergen Dust mite (Dpter-D far)	Clinic
	Dahl, 2006 ⁶³ Europe	SLIT (T) Placebo	Asthma diagnosis GINA criteria Severity Moderate persistent Control status NS	SPT and IgE wheal >3mm IgE NS	Monosensitized Grass mix	Single allergen Grass mix	Home
	Calderon, 2006 ⁶⁴ Europe	SLIT (A) Placebo	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Controlled asthma	SPT and IgE wheal >3mm IgE > class 2	Monosensitized Grass (Phleum pratense)	Single allergen Grass (Phleum pratense)	Not specified

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Marogna, 2013 ⁶⁵ Europe	SLIT (T) Pharmacotherapy	Asthma diagnosis GINA criteria Pulmonary tests (Positive methacholine challenge -PD20 FEV1 <800g) Severity Mild persistent Control status Poorly controlled	SPT and IgE Skin test >5mm (does not specify if wheal or flare); and class II positivity to birch assessed with ImmunoCAP (Unicap)	Monosensitized Trees (Birch)	Single allergen Birch	Home
	Voltolini 2010 ⁶⁶ Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria Severity Moderate to severe Control status NR	SPT and IgE NS	Monosensitized White birch	Single allergen Birch	NS
	Marogna, 2009 ⁶⁷ Europe	SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria – FEV 60-80%) Severity Moderate Control status controlled	SPT Wheal >5mm	Monosensitized White birch	Single allergen Birch	NS
	Marogna, 2010 ⁶⁸ Europe	SLIT (A) Pharmacotherapy	Asthma diagnosis GINA criteria – FEV>79%) Severity Mild Control status controlled	SPT and IgE Wheal >5mm IgE class 2	Monosensitized Grass mix	Single allergen Grass mix	NS
Children and adults	Pham-Thi, 2007 ⁶⁹ Europe	SLIT (T) Placebo	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation) Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE level ≥ 2 CAP RAST	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified
	Bahceciler, 2001 ⁷⁰ Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>79%) Severity Mild Control status controlled	SPT and IgE Wheal >5mm IgE class 2	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified
	La Grutta, 2007 ⁷¹	SLIT (T) Pharmacotherapy	Asthma diagnosis criteria NS Severity NS Control status NS	SPT >3mm	Both mono and polysensitized Not reported	Single allergen Dust mite (NS)	Home
Children	Lue, 2006 ⁷² Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified
	Niu, 2006 ⁷³ Asia	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE > 3	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified
	Ippoliti, 2003 ⁷⁴ Europe	SLIT (A) Placebo	Asthma diagnosis GINA criteria – FEV>70%) Severity Mild- moderate persistent Control status controlled	SPT and IgE Wheal >5mm IgE class 3	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified

T: Tablet

A: Aqueous

SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

Table 2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex % Male/Female	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Virchow, 2016 ⁵⁶	834	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	34 +/- 12 (Range 18-75) 34 +/- 12 (Range 17-74) 33 +/- 12 (Range 17-74)	48/52 52/48 55/45	257/34 282/43 277/48	NR
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	604	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	NR	NR	156/16 159/25 146/14 143/17	12 weeks
	Maloney, 2016 ⁶⁰	195	SLIT (T) 6 SQ HDM SLIT (T) 12 SQ HDM Placebo	14 +/- 2 14 +/- 2	60/40 62/38	65/5 65/4 65/0	6 months
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	484	SLIT (A) Placebo	31 +/- 9 (Range 14-50) 31 +/- 8 (Range 16-49)	27/73 42/58	322/14 162/4	1 year
	Dahl, 2006 ⁶³	114	SLIT (T) Placebo	36.5 34.1	71/29 60/40	74/13 40/8	14 12
	Calderon, 2006 ⁶⁴ Europe	43	SLIT (A) (4 doses) VS. placebo	25 +/- 6 (Range 18-42) 24 +/- (Range 21-40)	66/34 55/45	32/0 11/0	2 years
	Marogna, 2013 ⁶⁵	84	SLIT (T)+ Budesonide 400 µg Budesonide 800 µg Budesonide 1600 µg Budesonide 400 µg + ALKT	NR	NR	21/2 21/3 21/1 21/2	2 years
	Voltolini, 2010 ⁶⁶	24	SLIT (A) Placebo	44+/- 9 40 +/ - 7	50/50 30/70	14/1 10/1	NR
	Marogna, 2009 ⁶⁷	51	SLIT (A) Pharmacotherapy	27 +/- 1 (Range 17-41) 27 +/- 1 (Range 19-41)	44/56 46/54	25/2 26/3	8 7
	Marogna, 2010 ⁶⁸	33	SLIT (A) Pharmacotherapy	NR	NR	17/1 16/3	2 years
Children and adults	Pham-Thi, 2007 ⁶⁹	111	SLIT (T) Placebo	9.6 (Range 5-14) 9.5 (Range 5-16)	72/28 72/28	54/11 54/8	5
	Bahceciler, 2001 ⁷⁰	15	SLIT (A) Placebo	Median 12 (Range 8-18) Median 12 (Range 7-15)	50/50 58/43	8/0 7/0	Median 1.5 Median 3
	La Grutta, 2007 ⁷¹	56	SLIT (T) Pharmacotherapy	15 +/- 9 (Range 8-44) 22 +/- 15 (Range 7-68)	67/33 56/44	33/0 23/0	NR
Children	Lue, 2006 ⁷²	20	SLIT (A) Placebo	7.7 +/- 1.8 8.6 +/- 1.8	40/60 40/60	10/0 10/0	1
	Niu, 2006 ⁷³	110	SLIT (A) Placebo	7.9 +/- 1.6 (Range 5-11) 8.2+/- 1.7 (Range 5-12)	61/39 58/42	56/7 54/6	1
	Ippoliti, 2003 ⁷⁴	86	SLIT (A) Placebo	Median;9 (Range 5-12) Median;9 (Range 7-11)	60/41 56/44	47/0 39/0	2 2

T: Tablet A: Aqueous NR: Not reported

Table 3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Virchow, 2016 ⁵⁶	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Only rescue (ICS)	6 SQ-HDM 12 SQ-HDM	360 SQ/ month 720 SQ /month	Daily	NR	7-12 months
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	Only rescue (ICS and B2)	6 SQ-HDM 3 SQ-HDM 1 SQ-HDM	NR	Daily	NR	1 year
	Maloney, 2016 ⁶⁰	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Only rescue (ICS)	6 SQ-HDM 12 SQ-HDM	168 SQ 336 SQ	Daily	NR	28 days
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	SLIT (A) Placebo	Both (Budesonide, Salbutamol, Prednisone)	300 IR	NR	Daily	28ug Der p 1 and 50 ug Der f 1	52 weeks
	Dahl, 2006 ⁶³	SLIT (T) Placebo	Both (NS)	7500 SQT	NR	Daily	15 phl p5	137 days (Ultragrush)
	Calderon, 2006 ⁶⁴	SLIT 75000 (T) SLIT 150000 (T) SLIT 300000 (T) SLIT 500000 (T) Placebo	NR	75000 SQT 150000 SQT 300000 SQT 500000 SQT	NR	Daily	15 ug /dose 30 ug /dose 60 ug /dose 100 ug /dose	28 days
	Marogna, 2013 ⁶⁵	SLIT (T)+Budesonide 400µg Budesonide 800 µg Budesonide 1600 µg Budesonide 400 µg + LTRA	ICS BID Montelukast only for arm 4 No other treatment allowed	Pre-coseasonal	60,000 AU	1000 AU day/ 5 days a week for 12 weeks/ season for 3 years	60,000 AU (214,200µg of modified major allergen)	3 years
	Voltolini 2010 ⁶⁶	SLIT (A) Placebo	Conventional therapy	300 IR	13.8 IR per season	Daily	13.8 IR (6.9 µgBet v1 per season)	4 months
	Marogna, 2009 ⁶⁷	SLIT (A) Pharmacotherapy	Conventional therapy	5 drops of 10,000 RU/ml	70 µg (yearly)	3 times a week	70 Phl p1 (per year)	5 years
	Marogna, 2010 ⁶⁸	SLIT (A) Pharmacotherapy	Conventional therapy (Formoterol/ Fluticasone)	5 drops of 10,000 RU/ml	NR	3 times a week	100 µg Bet v 1 per year	5 years
Mixed age	Pham-Thi, 2007 ⁶⁹	SLIT (T) Placebo	Both (ICS and B2)	300 IR	155,000 IR	Daily	6.9mg Der p 1 and 14.7mg Der f 1	18 months
	Bahceciler, 2001 ⁷⁰	SLIT (A) Placebo	Conventional therapy	20 drops of 100 IR/mL	7000 IR	daily 4 weeks, then 2 times a week for 4 months	560 Der P, 980 Der F (cumulative)	6 months
	La Grutta, 2007 ⁷¹	SLIT (T) Pharmacotherapy	Only rescue (ICS)	Rush 1000 AU	NR	Biweekly	NR	1 year
Children	Lue, 2006 ⁷²	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/mL	41824 IR	Daily	3 mg Der F 1.7 mg Der P (Cumulative)	24 weeks

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Niu, 2006 ⁷³	SLIT (A) Placebo	Conventional and rescue as needed	20 drops of 300 IR/ml	41824 IR	Daily	3 mg Der F, 1.7 mg Der P (Cumulative)	24 weeks
	Ippoliti, 2003 ⁷⁴	SLIT (A) Placebo	Conventional therapy	5 drops of 10 BU/mL	NR	3 times a week	2.4 Der p1 1.2 Der p2 (per week)	6 months

T: Tablet A: Aqueous BU: Biological units SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit µg: microgram Ag/ml: major protein unit
 TU: Treatment units wt/vol Weight to volume SE: Specific units of short-term immunotherapy IR: Index of reactivity unit LTRA: Leukotriene receptor antagonist

Table 4 – Asthma Control

Study	Allergen and Asthma Severity	Arms	N	Outcome Description	Time of Measure	Value Pre	Value post	Comparative Values
Virchow, 2016 ⁵⁶	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 282 277	ACQ	12 months	Mean (SD) [IQR] 1.24 (0.17) [0.86-1.71] 1.23 (0.17) [0.71-1.57] 1.22 (0.18) [0.86-2.00]	Improvement 218 (78.88%) 221 (80.63%) 232 (83.02%)	OR (95% CI): 6SQ-HDM vs placebo 1.12 (0.73 to 1.70) 12SQ-HDM vs placebo 1.31 (0.85 to 2.01) P = 0.22
de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	ACQ	12 months	Mean score 1.15 1.16 1.21 1.20	Change within group -0.41 -0.22 -0.16 0	SLIT 6SQ-HDM pre vs post P=0.0002
Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	Dust mite Mild and moderate	SLIT (A) Placebo	113 62	ACQ	52 weeks	1.81 +/- 0.88 1.78 +/- 0.90	Percentage improvement 56.6% 40%	SLIT vs Placebo P<0.039
Marogna, 2013 ⁶⁵	Birch Mild asthma	SLIT(T)+Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	19 19 20 18	ACT	3 years	Mean 14.1 16.1 15.3 13.4	Mean 24 17.2 19.1 18.4	SLIT vs all other arms P<0.05

ACT: Asthma control test ACQ: Asthma control questionnaire SQ-HDM: standard quality house dust mite tablet LTRA: Leukotriene receptor antagonist SLIT vs comparator post data unless otherwise noted

Table 5 – Quality of Life

Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (AQLQ)

No study reported on Asthma QOL using Pediatric Asthma Specific Quality of Life – Asthma Quality of Life Questionnaire (PAQLQ)- School/Work Absences

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post
Virchow, 2016 ⁵⁶	Dust mite Moderate to severe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	275 285 277	12 months	Mean +/- SD 5.46 +/- 0.88 5.49 +/- 0.78	Improvement 231 (84.98%) 236 (84.39%)	6SQ-HDM vs placebo post OR (95% CI); 1.01 (0.63- 1.62) 12SQ-HDM vs placebo post

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post
					5.54 +/- 0.78	233 (84.80%)	OR (95% CI): 0.97 (0.61- 1.53) P = 0.89
de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	29 27 25 27	12 months	5.62 5.58 5.75 5.52	Change within group + 0.52 + 0.32 + 0.30 0	SLIT 6SQ-HDM pre vs post P=0.01 Other arms NR Between arms comparisons NR
Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	Dust mite Mild and moderate	SLIT (A) Placebo	13 62	52 weeks	Mean +/- SD 4.6 +/- 1.0 4.5 +/- 1.1	Mean +/- SD 6.0 +/- 0.9 5.9 +/- 0.9	NR

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

NR: Not reported

Table 6 – Medication Use**A. Quick Relief Medication**

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Marogna, 2009 ⁶⁷	Birch Moderate asthma	SLIT (A) Pharmacotherapy (montelukast)	5 6	5 years	SABA, (Doses used over 3 month period)	20.1 +/- 0.7 19.4 +/- 0.9	4.0 +/- 0.9 15.8 +/- 1.0	SLIT pre vs post P<0.01, pharm pre vs post P=0.019 SLIT vs pharm P<0.001
Marogna, 2013 ⁶⁵	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	SABAS (doses used over 3 month period)	Mean +/- SE 11.1 +/- 0.6 11.1 +/- 0.6 11.2 +/- 0.6 11.9 +/- 0.9	Mean +/- SE 1 +/- 0.2 10.4 +/- 1.2 8.3 +/- 1.3 7.4 +/- 1.1	SLIT vs all budesonide control groups P <0.001
Marogna, 2010 ⁶⁸	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (budesonide)	17 16	5 years	SABA (doses over 3 month period)period	23.0 +/- 1.5 22.4 +/- 0.9	5.1 +/- 1.4 13.0 +/- 1.2	SLIT vs budesonide P<0.001
Niu, 2006 ⁷³	Dust mite Mild- moderate asthma	SLIT (A) Placebo	56 54	24 weeks	Inhaled B agonist (puff/ day)	Mean (SD) SLIT: 0.06 (0.09) Placebo: 0.03 (0.01)	Mean (SD) SLIT: 0.02 (0.31) Placebo:0.05 (0.27)	SLIT pre vs. post P= 0.371 Placebo pre vs. post P= 0.185 SLIT vs. placebo change from baseline P= 0.951

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

LTRA: Leukotriene receptor antagonist

unless otherwise noted

NR: Not reported

SLIT vs comparator post data

B. Long Term Control Medication

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	52 weeks	Inhaled corticosteroid (ICS) Absolute decrease in budesonide dose	NR NR	218.5 126.5	SLIT vs placebo post P = 0.004

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	Dust mite Mild and moderate	SLIT (T) 6 SQ-HDM SLIT (T) 3 SQ-HDM SLIT (T) 1 SQ-HDM Placebo	156 159 146 143	6 months	Inhaled corticosteroid (ICS) Average daily use (µg)	541 648 636 641	-327 -75 -103 -50	SLIT 6HQ-HDM pre vs post <i>P</i> < 0.05
Pham-Thi, 2007 ⁶⁹	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	Use of inhaled steroids (ICS) (Budesonide) µg/day	Mean +/- SD 548 +/- 220 534 +/- 237	Mean +/- SD 257 +/- 232 223 +/- 270	NR
Niu, 2006 ⁷³	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	ICS (puff/ day)	Mean (SD) SLIT: 0.6 (1.14) Placebo: 0.47 (0.84)	Mean (SD) SLIT: 0.43 (1.09) Placebo: 0.37 (0.86)	change from baseline SLIT pre vs. post <i>P</i> = 0.782 Placebo pre vs. post <i>P</i> = 0.522 SLIT vs. placebo <i>P</i> = 0.215

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

LTRA: Leukotriene receptor antagonist

NR: Not reported

C. Systemic Corticosteroids

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Niu, 2006 ⁷³	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	Oral steroids (tablet/day)	Mean (SD) SLIT: 0.11(0.35) Placebo: 0.04(0.15)	Mean (SD) SLIT: 0.03(0.22) Placebo: 0.04(0.22)	Change from baseline SLIT pre vs post <i>P</i> = 0.183 Placebo pre vs. post <i>P</i> = 1.000 SLIT vs. placebo <i>P</i> = 0.195

SLIT vs comparator post data unless otherwise noted

Table 7 – Asthma Exacerbations

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Virchow, 2016 ⁵⁶	Dust mite Moderate to severe	SLIT 6 SQ-HDM SLIT12 SQ-HDM Placebo	275 285 277	6 months	Time to asthma exacerbation	NR	HR (95% CI) 0.72 (0.52-0.99) 0.69 (0.50- 0.96)	SLIT(T) 6 SQ-HDM vs placebo <i>P</i> =0.045 SLIT(T) 12 SQ-HDM vs placebo <i>P</i> =0.03
					Time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings	NR	HR (95% CI) 0.72 (0.49-1.07) 0.64 (0.42- 0.96)	SLIT(T) 6 SQ-HDM vs placebo <i>P</i> = 0.17 SLIT(T) 12 SQ-HDM vs placebo <i>P</i> =0.03
					Time to first asthma exacerbation with deterioration in lung	NR	HR (95% CI) 0.60 (0.38- 0.95) 0.52 (0.29- 0.94)	SLIT(T) 6 SQ-HDM vs placebo <i>P</i> = 0.03 SLIT(T) 12 SQ-HDM vs placebo <i>P</i> =0.02

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
					function			
					Time to first asthma exacerbation with increased use of SABA	NR	HR (95% CI) 0.62 (0.36- 1.07) 0.52 (0.29- 0.94)	SLIT(T) 6 SQ-HDM vs placebo $P= 0.09$ SLIT(T) 12 SQ-HDM vs placebo $P=0.03$
					Time to first severe asthma exacerbation	NR	HR (95% CI) 0.72 (0.52- 0.99) 0.69 (0.50- 0.96)	SLIT(T) 6 SQ-HDM vs placebo $P= 0.03$ SLIT(T) 12 SQ-HDM vs placebo $P=0.02$
de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	Dust mite Mild and moderate	SLIT 6 SQ-HDM (T) SLIT 3 SQ-HDM (T) SLIT 1 SQ-HDM (T) Placebo	156 159 146 143	year	Number of asthma exacerbations	NR	NR	Not a statistical significance for either of the treatment groups or the placebo groups

T: Tablet

A: Aqueous

SQ-HDM: standard quality house dust mite tablet

LTRA: Leukotriene receptor antagonist

NR: Not reported

SLIT vs comparator post data unless otherwise noted

Table 8 – Healthcare Utilization

No study reported on Healthcare Utilization; Asthma Specific Hospitalizations, Emergency Department (ED) or Outpatient visits, Asthma Specific ICU admissions or intubations.

Table 9 – Pulmonary Physiology

A. PEF

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Lue, 2006 ⁷²	Dust mite Mild asthma	SLIT (A) Placebo	10 10	6 months	PEF	NR	NR	SLIT pre vs post improved $P=0.0088$, in the evening but not in am. Placebo pre vs post NS SLIT vs Placebo post NS
Pham-Thi, 2007 ⁶⁹	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	PEF	Mean +/- SD 8.03 +/- 7.21) 7.48 +/- 6.14)	Mean +/- SD 6.06 +/- 5.45 6.36 +/- 5.65	NR
Calderon, 2006 ⁶⁴	Phleum pratense Mild and moderate	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	32 11	NR	PEF	NR	NR	No clinically significant changes were observed
Niu, 2006 ⁷³	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	PEF	NR	NR	SLIT pre vs. post $P= 0.001$ Placebo pre vs. post NS SLIT vs placebo NS

T: Tablet

A: Aqueous

SQ-T: standard quality tablet

PEF: Peak expiratory flow

NR: Not reported

NS: Not significant

B. FEV₁

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	Dust mite Mild and moderate	SLIT (A) Placebo	322 164	52 weeks	FEV1	NR	NR	The mean FEV1% predicted remained above 80% during the treatment period in both SLIT and placebo groups. No significant difference
Niu, 2006 ⁷³	Dust mite Mild asthma	SLIT (A) Placebo	56 54	24 weeks	FEV1	85 90	95 90	SLIT pre vs post P=0.048 Placebo pre vs post NS SLIT vs Placebo NS
Ippoliti, 2003 ⁷⁴	Dust mite Mild- moderate asthma	SLIT (A) Placebo	47 39	6 months	FEV1	83.4 80.7	92.6 81.2	SLIT pre vs post P< 0.001 Placebo pre vs post P NS SLIT vs Placebo NR
Lue, 2006 ⁷²	Dust mite Mild- moderate asthma	SLIT (A) Placebo	10 10	6 months	FEV1	NR	NR	SLIT pre vs post improved P=0.01 Placebo P =0.48 SLIT vs Placebo = 0.929
Marogna, 2010 ⁶⁸	Grass mix Mild asthma	SLIT (A) Pharmacotherapy (Montelukast)	17 16	5 years	FEV1	78.5(1.0) 76.4 (1.3)	96.2(1.2) 81.2(1.4)	SLIT vs Pharm P<0.0001
Marogna, 2013 ⁶⁵	Birch Mild asthma	SLIT (T) + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + LTRA	21 21 21 21	3 years	FEV1	Mean +/- SE 85.2 +/- 0.6 88.3 +/- 0.8 87 +/- 0.8 86.2 +/- 0.6	Mean +/- SE 103.3 +/- 1.5 90.3 +/- 2.1 92.4 +/- 2.0 96.5 +/- 2.9	SLIT vs all other arms P<0.05
Calderon, 2006 ⁶⁴	Phleum pratense Mild and moderate	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	32 11	NR	FEV1	NR	NR	No clinically significant changes were observed
Pham-Thi, 2007 ⁶⁹	Dust mite Mild and moderate	SLIT (T) Placebo	54 54	18 months	FEV1	Mean +/- SD 91.9 +/- 3.4 95.1 +/- 15.1	Mean +/- SD 88.5 +/- 13.4 94.5 +/- 14.6	SLIT vs placebo post NS
de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	Dust mite Mild and moderate	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	156 159 146 143	1 year	FEV1	NR	NR	SLIT versus placebo post NS

T: Tablet

A: Aqueous

SQ-T: standard quality tablet

FEV: Flow expiratory volume

NR: Not reported

NS: Not significant

C. FVC

Study	Allergen and Asthma Severity	Arms	N	Time of Measure	Outcome Description	Value Pre	Value post	Comparative Values
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Niu, 2006 ⁷³	Dust mite Mild – moderate asthma	SLIT (A) Placebo	56 54	24 weeks	FVC	NR	NR	SLIT pre vs post $P=0.042$ Placebo pre vs. post- NS SLIT vs placebo post NS
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A: Aqueous

NR: Not reported

NS: Not significant SLIT vs comparator post data unless otherwise noted

Table 10 – Airway Hyperresponsiveness AHR**A. Methacholine Challenge**

Study	Allergen and Asthma Severity	Arms	Time of measure	N	Outcome Description	Units Value Pre	Value post	Comparative Values
La Grutta, 2007 ⁷¹	Dust mite Severity NS	SLIT (A) pharmacotherapy	1 year	33 23	AHR- PD20 FEV1	µg of methacholine Mean +/- SD 626.4 +/- 526.19 616.1 +/- 578.08	µg of methacholine Mean +/- SD 1277.7 +/- 963.51 860.3 +/- 732.39	SLIT pre vs post $P = 0.001$ Pharm pre vs post $P = 0.08$ SLIT vs pharm not reported
Marogna, 2010 ⁶⁸	Birch Mild asthma	SLIT (A) Pharmacotherapy (Montelukast)	5 years	17 16	AHR- PD20 FEV1	µg of methacholine Mean +/- SD 326.4(50.1) 288.6(44.9)	µg of methacholine Mean +/- SD 919.3(85.7) 478.7 (76.2)	SLIT pre vs post $P < 0.001$; Mont pre vs post $P = 0.019$ SLIT vs Mont $P = 0.001$
Marogna, 2013 ⁶⁵	Birch Mild asthma	SLIT + Budesonide Budesonide 800 µg Budesonide 1600 µg Budesonide + ALKT	3 years	21 21 21 21	AHR- PD20 FEV1	µg of methacholine Mean +/- SE 166.8(18.3) 199.8(24.7) 226.9(22.6) 165.7(17.0)	µg of methacholine Mean +/- SE 997.1(39.7) 644.9(89.3) 520.0(64.7) 728.7(76.0)	SLIT vs all other arms $P < 0.05$

T: Tablet

A: Aqueous

µg:micrograms

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

PD20: Concentration of allergen causing a fall of 20% in FEV1

B. Allergen Challenge

No study measured allergen challenges

C. Exercise Challenge

No study measured exercise challenges

Table 11 – Immunologic Parameters**A. IgE**

Study	Allergen	Arms	Time of Measure	Outcome/ Units	Baseline Values	Final Values	Comparative Values
Devillier, 2016 ⁶¹	Dust mite (Dpter-Dfar)	SLIT tablet Placebo	52 weeks	Specific IgE to Dpter kU/L	Mean – [IQR] Dpter 28.7 [24.7-33.4] 30.3 [24.7-37.3] Dfar 26.4 [22.7-30.6]	geometric mean fold-change Dpter 1.58 Dfar NR	SLIT pre vs post 95%CI [1.44-1.74] Placebo pre vs post NS changes

Study	Allergen	Arms	Time of Measure	Outcome/ Units	Baseline Values	Final Values	Comparative Values
					26.3 [21.3-32.4]		
Lue, 2006 ⁷²	Dust mite (Dpter-Dfar)	SLIT aqueous Placebo	6 months	Specific IgE to Dpter IU/L	Mean 500 400	Increased Did not change	No significant change
Niu, 2006 ⁷³	Dust mite (Dpter-Dfar)	SLIT aqueous Placebo	24 weeks	Specific IgE to Dpter KU/L	Mean 829.8 780.6	Change 129 +/- 460 -85.+-59.8	SLIT vs placebo post P=0.063
Bahceciler, 2001 ⁷⁰	Dust mite (Dpter-Dfar)	SLIT aqueous Placebo	6 months	Specific IgE to Dpter KU/L	Median (range) 420 (42-2751) 405 (197-5967)	Median (range) 295 (40-1701) 536 (166-3948)	No significant difference
Pham-Thi, 2007 ⁶⁹	Dust mite (Dpter-Dfar)	SLIT tablet Placebo	18 months	Specific IgE to Dpter KU/L	Mean (SD) 208 (38) 197 (30)	Mean (SD) 250 (36) 135 (21)	NR
Tian, 2014 ⁷⁵	Dust mite (Dfar)	SLIT aqueous Placebo	48 weeks	Specific IgE to Dpter KU/L	Specific IgE Grading n(%) Grade II 4 (13.3) 5 (16.7) Grade III 14 (46.7) 13 (43.3) P = 0.95	No changes	NS changes

T: Tablet

A: Aqueous

 μ :microgramsDpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

B. IgG4

Study	Allergen	Arms	Outcome Description	Time of Measure	Baseline Values	Final values	Comparative values
Virchow, 2016 ⁵⁶	Dust mite (Dpter-Dfar)	SLIT 6 SQ HDM SLIT 12 SQ HDM Placebo	D pter 1 specific IgG4 (mgA/L)	NR	Mean (SD) [range] 0.4 (0.4) [0.0-3.3] 0.4 (0.6) [0.0-6.4] 0.5 (0.5) [0.0-3.4]	0.425 (0.022) 0.558 (0.024) -0.037 (0.014)	SLIT 6 vs Placebo post P < 0.001 SLIT 12 vs Placebo post P < 0.001
			D far specific IgG4 (mgA/L)		Mean (SD) [range] 0.4 (0.3) [0.0-2.7] 0.5 (0.9) [0.0-9.8] 0.4 (0.5) [0.0-3.7]	0.404 (0.022) 0.540 (0.026) -0.054 (0.015)	SLIT 6 vs Placebo post P < 0.001 SLIT 12 vs Placebo post P < 0.001
Devillier, 2016 ⁶¹	Dust mite (Dpter-Dfar)	SLIT - Dpt-Dfar Placebo	Dpter p 1 specific IgG4	NR	NR	geometric mean fold-change Dpter 1.99 Dfar NR	SLIT pre vs post 95%CI [1.81-2.18] Placebo pre vs post NS changes SLIT vs placebo NR
Pham-Thi, 2007 ⁶⁹	Dust mite (Dpter-Dfar)	SLIT tablet Placebo	IgG4 antibody assay, (μ g/l)	18 months	Mean (SD) (ug/ml) 1166 (188) 761 (73)	Mean (SD) (ug/ml) 4462 (860) 650 (51)	SLIT pre vs post P < 0.001 Placebo pre vs post NS SLIT vs placebo post NR
Lue, 2006 ⁷²	Dust mite (Dpter-Dfar)	SLIT aqueous Placebo	NR	Specific IgE to Dpter IU/L	NR	NR	Statistically significant increase within group and when compared to placebo P=0.026

T: Tablet

A: Aqueous

 μ :microgramsDpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

C. Allergy Skin Testing

Study	Allergen	Arms	Time of Measure	Outcome Description	Baseline Values	Final values	Comparative values
Devillier, 2016 ⁶¹	Dust mite (Ppter-Dfar)	SLIT tablet Placebo	50 weeks	Wheal size mm	mean (SD) Dpter 8.9 (5.4) Dfar 8.5 (4.9) Dpter 9.1 (5.5) Dfar 9.0 (5.9)	change mean (SD) Dpter -2.8 (5.4) Dfar -2.9 (4.7) Dpter -1.4 (5.4) Dfar -1.8 (6.3)	SLIT pre vs post $P < 0.0001$ Placebo pre vs post NR
Pham-Thi, 2007 ⁶⁹	Dust mite (Dpter-Dfar)	SLIT tablet Placebo	18 months	Skin wheal diameter	Mean 5.31 5.81	Mean 2.9 5.3	SLIT pre vs post difference -2.15 Placebo pre vs post difference -0.46 SLIT vs placebo $P < 0.001$
Tian, 2014 ⁷⁵	Dust mite (Dfar)	SLIT aqueous Placebo	48 weeks	Specific Skin prick test	n(%) 2+ 16 (53.3) 15 (50.0) 3+ 14 (46.7) 15 (50.0) $P = 0.79$	No changes	NS changes

T: Tablet

A: Aqueous

NS: Not significant

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

Table 12 – Other Outcomes - Compliance

Study	Allergen	Arms	N	Time of Measure	Outcome Description	Baseline Values	Final Values	Comparative Values
Maloney, 2016 ⁶⁰	Dust mite (Dpter-Dfar)	SLIT - 6 SQ-HDM (T) SLIT - 12 SQ-HDM (T) Placebo	22 24 22	14 days	mean compliance with study drug	NR	97 99 98	NR
de Blay, 2014 ³⁷	Dust mite (Dpter-Dfar)	SLIT 6-HQ HDM (T) SLIT 3-HQ HDM (T) SLIT 1-HQ HDM (T) Placebo	134 131 117 107	1 year	Number of non-compliant subjects	NR	4 (3%) 2 (2%) 3 (3%) 1 (1%)	NR
Devillier, 2016 ⁶¹	Dust mite (Dpter-Dfar)	SLIT (T) Placebo	308 157	52 weeks	Number of unused SLIT packs	NR	90.9% 93%	NR

T: Tablet

A: Aqueous

NR: Not reported

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

Appendix G: KQ4- What is the evidence for the safety of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

KQ4- What is the evidence for the safety of sublingual immunotherapy (SLIT) in tablet and aqueous form, in the treatment of asthma?

(Organization in tables first by population; adults-mixed population- children. Within each category by comparator SCIT vs placebo- SCIT vs pharmacotherapy- SCIT vs SCIT. Within each subcategory by allergen; HDM-grass- weed- trees- animal-multiple allergen)

SECTION A SLIT Safety for RCTs

Table A.1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Virchow, 2016 ⁵⁶ Europe	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Moderate to severe Asthma Pulmonary tests (PFT reversibility) Poorly Controlled	SPT and IgE SPT ≥ 3 mm SIgE ≥ 0.70 kU/L	Both Mono and Polysensitized “Patients could have multiple sensitization but no perennial asthma caused by other allergens”	Single allergen Dust mite (Dpter-D far)	Clinic
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹ Europe	SLIT(T) 6 SQ-HDM SLIT(T) 3 SQ-HDM SLIT(T) 1 SQ-HDM Placebo	Asthma diagnosis GINA criteria (steps 2 and 3) Pulmonary tests (documented history of reversible airway obstruction) Mild persistent and moderate persistent Controlled (ACQ scores and ICS dose of 100 to 800 mg/d)	SPT and IgE wheal size >3mm to D farinae, D pteronyssinus, or both IgE NS	Both Mono (17%) and Polysensitized (83%)	Single allergen Dust mite (Dpter-D far)	Not specified
	Maloney, 2016 ⁶⁰ US	SLIT(T) 6 SQ-HDM SLIT(T) 12 SQ-HDM Placebo	Asthma diagnosis GINA criteria Severity not specified Controlled (FEV1 ≥70% predicted, no more than 2 symptoms per week, no more than 2 days of SABA use per week, no more than 2 awakenings per month due to asthma)	SPT and IgE wheal diameter ≥5mm larger than saline control; serum-specific IgE ≥ 0.7 kU/L or at least class II (all against D pter or D far)	39 patients monosensitized Dust mite (Dpter-D far) 156 patients polysensitized grass, cat, dog, mold, birch,mugwort	Single allergen Dust mite (Dpter-D far)	Home
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶² Multisite	SLIT (A) Placebo	Pulmonary tests (bronchial reversibility test and methacholine challenge) Mild persistent and moderate persistent	SPT and IgE wheal diameter ≥ 4 mm in an SPT after washout of antihistamines, specific IgE ≥ 0.70 kU/I	Polysensitized Dust mites (Dpter-D far), cat. dog	Single allergen Dust mite (Dpter-D far)	Clinic
	Dahl, 2006 ⁶³ Europe	SLIT (T) Placebo	Asthma diagnosis GINA criteria Severity Moderate persistent Contrul status NS	SPT and IgE wheal >3mm IgE NS	Monosensitized Grass mix	Single allergen Grass mix	Home
	Calderon,	SLIT (A)	Asthma diagnosis criteria NS	SPT and IgE	Monosensitized	Single allergen	Not

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	2006 ⁶⁴ Europe	Placebo	Severity Mild persistent and moderate persistent Controlled asthma	wheel >3mm IgE > class 2	Grass (<i>Phleum pratense</i>)	Grass (<i>Phleum pratense</i>)	specified
	Marogna, 2013 ⁶⁵ Europe	SLIT Pharmacotherapy	Asthma diagnosis GINA criteria Pulmonary tests (Positive methacholine challenge -PD20 FEV1 <800g) Severity Mild persistent Control status Poorly controlled	SPT and IgE Skin test >5mm (does not specify if wheal or flare); and class II positivity to birch assessed with ImmunoCAP (Unicap)	Monosensitized Trees (Birch)	Single allergen Birch	Home
	Shao, 2014 ⁷⁶ Asia	SLIT (A) Pharmacotherapy	Pulmonary tests (20% decrease in FEV1 following < 8mg methacholine/mL or reversibility of FEV1 > 15% after bronchodilator + clinical symptoms) Severity and control NS	SPT and IgE wheal size ≥3mm IgE ≥ 0.7	Polysensitized (Dpter-D far), cat, dog, german cockroach, artemisia pollen, humulus pollen, and plantain pollen)	Single allergen Dust mite (D far)	Clinic
Mixed age	Corzo, 2014 ⁷⁷ Europe	SLIT (T) SLIT	WHO/GINA criteria Mild persistent and moderate persistent Controlled	SPT and IgE wheal ≥3mm IgE ≥ class2	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	La Grutta, 2007 ⁷¹ Europe	SLIT (T) Pharmacotherapy	Asthma diagnosis criteria NS Severity NS Control status NS	SPT >3mm	Both mono and polysensitized Not reported	Single allergen Dust mite (NS)	Home
	Pham-Thi, 2007 ⁶⁹ Europe	SLIT (T) Control	Asthma diagnosis pulmonary tests (reversible bronchial obstruction – salbutamol inhalation) Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE level ≥ 2 CAP RAST	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Not specified
	Bufe, 2009 ⁷⁸ Europe	SLIT (T) placebo	Asthma diagnosis criteria GINA and FEV1<80% expected after treatment with ICS and SABA) Severity Mild persistent Control status NS	SPT and IgE wheal >3mm, serum specific IgE class 2	Monosensitized Timothy grass	Single allergen Timothy grass	NR
Children	Mosges, 2010 ⁷⁹ Europe	SLIT(A) OTHER	Asthma diagnosis criteria NS Severity Mild persistent and moderate persistent Control status NS	SPT and IgE SPT NS IgE ≥ 0.7 kU/L	Polysensitized tree pollens (birch alder and/or hazel)	Single allergen Birch	Not specified

T: Tablet A: Aqueous SPT: Skin prick test IgE:ImmunoglobulinE NS: Not specified Dpter: *Dermatophagoides pteronyssinus* Dfar: *Dermatophagoides farina*

Table A.2 – Patient Characteristics

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Virchow, 2016 ⁵⁶	834	SLIT 6 SQ HDM SLIT 12 SQ HDM Placebo	33.6 (12.2) 33.7 (11.6) 33 (12.2)	48/52 52/48 55/45	275/34 282/43 277/48	NR
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	604	SLIT 6 SQ-HQM SLIT 3 SQ-HQM SLIT 1 SQ-HQM Placebo	32 (NR) 32 (NR) 32 (NR) 32 (NR)	NR	156/16 159/25 146/14 143/17	NR
	Maloney, 2016 ⁶⁰	195	HDM SLIT 6 SQ-HDM HDM SLIT 12 SQ-HDM Placebo	14.5 (1.7) 14.5 (1.6) 14.3 (1.8)	60/NR 62/NR 68/NR	22/NR 24/NR 22/NR	NR
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	484	SLIT Placebo	31.2 (9) 31.3 (8.2)	46.8/53.2 41.4/58.6	308/23 157/8	12.8 years 13.7 years
	Dahl, 2006 ⁶³	114	SLIT (T) Placebo	36.5 34.1	71/29 60/40	74/13 40/8	14 12
	Calderon, 2006 ⁶⁴	43	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	22.1 (3.2) 23.2 (2.8) 28 (9.5) 25.8 (5.5) 24.5 (5.5)	67/33 67/33 67/33 60/40 55/45	9/0 9/0 9/0 9/0 11/0	12.9 years 15.7 years 22.2 years 19.4 years 15.4 years
	Marogna, 2013 ⁶⁵	84	SLIT+ BUD 400 µg/day BUD 800 µg/day BUD 1600 µg/day BUD 400 µg/day + LTRA	NR	NR	21/NR 21/NR 21/NR 21/NR	NR
	Shao, 2014 ⁷⁶	264	SLIT Pharmacotherapy	6.37 (.2) 5.92 (.31)	104/64 59/37	139/27 79/19	NR
Mixed age	Corzo, 2014 ⁷⁷ adults Corzo, 2014 ⁷⁷ Peds	71	SLIT 1 DU SLIT 2 DU SLIT 4 DU SLIT 8 DU SLIT 16 DU SLIT 16 DU Placebo	30.7(10.4) 32.4 (14.1) 25.9 (5.3) 30 (11.2) 27.9 (6) 25.2 (7.6) 29 (9.7)	33/67 22/78 33/67 56/44 44/56 22/78 47/53	54/NR 17/NR	Range: 13.8 years 14.8 years 13 years 17.1 years 16.1 years 15.8 years 0.2 years
	La Grutta, 2007 ⁷¹	56	SLIT Pharmacotherapy	15.4 (9) 21.8 (15)	22/11 13/10	33/0 23/0	NR
	Pham-Thi, 2007 ⁶⁹	111	SLIT Placebo	9.6 (NR) 9.5 (NR)	39/15 39/16	55/11 56/8	6.1 years 5.7 years
	Bufe, 2009 ⁷⁸	253	SLIT Placebo	Range: 5-16	NR	253/19	NR

Population	Study	Patients Randomized	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Children	Mosges, 2010 ⁷⁹	116	SLIT Placebo	10.2 (2.64) 10.5 (2.55)	37/63 67/33	27/NR 27/NR	NR

T: Tablet

A: Aqueous

NR: Not reported

SQU: standard quality tablet

SQ-HDM-T standard quality House dust mite tablet

Table A.3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Virchow, 2016 ⁵⁶	SLIT 6 SQ HDM T SLIT 12 SQ HDMT Placebo	Both	Targeted: 6 SQ Actual: 6 SQ Targeted: 12 SQ Actual: 12 SQ	Targeted: 360 SQ/month Actual: 360 SQ/month Targeted: 720 SQ/month Actual: 720 SQ/month	Daily	NR	7-12 months
	de Blay, 2014 ⁵⁷ Mosbech, 2014 ⁵⁸ Mosbech, 2015 ⁵⁹	SLIT 6 SQ-HQM SLIT 3 SQ-HQM SLIT 1 SQ-HQM Placebo	Rescue therapy	Targeted:6SQ Actual 6 SQ Targeted:3SQ Actual: 3 SQ Targeted:1SQ Actual: 1 SQ Targeted: NR Actual: NR	NR	Daily	NR	1 year
	Maloney, 2016 ⁶⁰	SLIT T 6 SQ-HDM SLIT T 12 SQ-HDM Placebo	Both	Targeted: 6 SQ-HDM Actual: 6 SQ-HDM Targeted: 12 SQ-HDM Actual: 12 SQ-HDM Targeted: NA Actual: NA	Targeted: 168 SQ Actual: 168 SQ Targeted: 336 SQ Actual:336 SQ Targeted: NR Actual: NR	Daily	NR	28 days
	Devillier, 2016 ⁶¹ Wang, 2014 ⁶²	SLIT Placebo	Both	Targeted: 300 IR Actual: 300 IR	NR	Daily	28ug Der p 1 and 50 ug Der f 1 NR	52 weeks: 24 w active treatment, 16 w step- down, 20 w efficacy measurement phase (8 w' overlap (between w 32 and 40)
	Dahl, 2006 ⁶³	SLIT (T) Placebo	Both (NS)	7500 SQT	NR	Daily	15 phl p5	137 days (Ultragush)

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Calderon, 2006 ⁶⁴	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	NR	Targeted: 75000 SQ-T Actual: 75000 SQ-T Targeted: 150000 SQ-T Actual: 150000 SQ-T Targeted: 300000 SQ-T Actual: 300000 SQ-T Targeted: 500000 SQ-T Actual: 500000 SQ-T Targeted: NR Actual: NR	NR	Daily	15 µg/dose 30/dose 60/dose 100/dose NR	28 days
	Marogna, 2013 ⁶⁵	BUD 400 µg/day + SLIT BUD 800 µg/day BUD 1600 µg/day BUD 400 µg/day + LTRA	Both	Targeted: 1000 AU once a day for five days/week Actual: 1000 AU once a day for five days/week	Targeted: Annual average dose approximately 60,000 AU Actual: Annual average dose approximately 60,000 AU Targeted: NR Actual: NR Targeted: NR Actual: NR	Daily	214,200 µg of protein (Annual cumulative) NR NR NR	12 weeks
	Shao, 2014 ⁷⁶	SLIT aqueous Pharmacotherapy	NR	NR	Targeted: .5 Actual: .5 Targeted: NR Actual: NR	Daily	NR	12 months
Mixed age	Corzo, 2014 ⁷⁷ adults Corzo, 2014 ⁷⁷ Peds	SLIT 1 DU SLIT 2 DU SLIT 4 DU SLIT 8 DU SLIT 16 DU SLIT 16 DU Placebo	NR	Targeted: 1 to 32 DU Actual: NR Targeted: NR Actual: NR	NR	NR	NR	28 days
	La Grutta, 2007 ⁷¹	SLIT Pharmacotherapy	Conven- tional therapy	Targeted: 1,000 AU Actual: 1,000 AU	NR	Biweekly NR	NR	1 year
	Pham-Thi, 2007 ⁶⁹	SLIT Placebo	Both	Targeted: 300 IR Actual: 300 IR Targeted: NR Actual: NR	Targeted: NR Actual: 155,000 IR, corresponding to 6.9mg Der p 1 and 14.7mg Der f 1 Targeted: NR Actual: NR	Daily NR	Daily dose: DerP1 27µg, Der f1 57µg	18 months
	Bufe, 2009 ⁷⁸	SLIT Placebo	Both	NR	NR	NR	NR	NA

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Children	Mosges, 2010 ⁷⁹	SLIT Placebo	Both	Targeted: 300 IR within 90 minutes Targeted: NR Actual: NR	NR	NR	NR	6 months

T: Tablet A: Aqueous BU: Biological units
 TU: Treatment units wt/vol Weight to volume SQU: standard quality units PNU: Protein Nitrogen Unit AU Allergy unit
 SE: Specific units of short-term immunotherapy IR: Index of reactivity unit µg: microgram NR: Not reported Ag/ml: major protein unit DU dosing unit

Table A.4 - Hypersensitivity

No studies reported specifically on hypersensitivity reactions, however all local, systemic, anaphylactic, and some of the “other” reactions should be noted to fall under the umbrella of hypersensitivity reactions.

Table A.5 – Local Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Pruritis/swelling of mouth, tongue or lip	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Oral pruritus Treatment related	37 (13) 55 (20) 8 (3)	45 78 8	0.14
					Edema mouth Treatment related	24 (9) 28 (10) 0 (0)	26 35 0	0.0
					Tongue pruritus Treatment related	12 (4) 13 (5) 1 (1)	13 15 1	0.437
					Swollen tongue Treatment related	1 (1) 5 (2) 0 (0)	1 6 0	0.0
					Laryngeal edema [moderate, no airway obstruction or dyspnea]	0 1 0	NR	0.0
	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	322 162	Swollen tongue	85 (26.4%) 2 (1.2%)	NR NR	0.252
					Oral pruritus	75 (23.3%) 23 (14.2%)	NR NR	0.091
					Glossitis	64 (19.9%) 17 (10.5%)	NR NR	0.094
					Mouth Edema	26 (8.1%) 0 (0)	NR NR	0.081
	de Blay, 2014 ⁵⁷	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	29 27 25 27	Mouth edema	8% 3% 2% 0%	NR NR NR NR	0.13

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Oral Irritation					oral pruritus	19%	NR	0.47
						19%	NR	
	Pham-Thi, 2007 ⁶⁹	Dust mite Intermittent, Mild and Moderate asthma	SLIT tablet Placebo	54 55	mouth itching/lip swelling	12%	NR	NA
						3%	NR	
	Calderon, 2006 ⁶⁴	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Mouth edema	3 (33) 1 (11) 2 (22) 0 0	3 1 4 NR NR	0.18
						6 (67) 9 (100) 8 (89) 5 (100) 4 (36)	13 49 96 77 5	
					Swollen tongue	1 (11) 0 1 (11) 1 (20) 0	1 NR 1 1 NR	0.093
	Dahl, 2006 ⁶³	Timothy Grass Mild and Moderate asthma	SLIT (T) Placebo	61 32	Oral pruritus	53% 5%	NR NR	0.5
	Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Oral pruritis	NR NR	277 0	NA
					Mouth edema	NR NR	90 0	NA
	Corzo, 2014 ⁷⁷ (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Oral pruritis	NR NR	263 5	NA
					Mouth edema	NR NR	96 0	NA
Throat Irritation	de Blay, 2014 ⁵⁷	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	29 27 25 27	throat irritation	6% 4% 2% 1%	NR NR NR NR	0.0
						6% 3% 1% 0.5%	NR NR NR NR	

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)	
Virchow, 2016 ⁵⁶ Calderon, 2006 ⁶⁴ Calderon, 2006 ⁶⁴ Dahl, 2006 ⁶³ Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Severity NS	Grass Mild and Moderate asthma	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Throat irritation Treatment related	21 (8) 27 (10) 4 (1)	26 32 4	0.07	
					Throat irritation	0 0 1 1 1	NR NR NR NR NR	-0.03	
	Calderon, 2006 ⁶⁴		SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Dry throat	2 (22) 0 0 1 (20) 0	4 NR NR 1 NR	0.09	
					Oral Hypoesthesia	0 0 1 (11) 3 (60) 0	NR NR 4 11 NR	0.09	
					Odynophagia	0 0 1 (11) 0 0	NR NR 1 NR NR	0.03	
	Calderon, 2006 ⁶⁴		SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Dysphagia	0 0 1 (11) 0 0	NR NR 2 NR NR	0.03	
					Pharyngitis	3 (33) 0 4 (44) 0 1 (9)	3 NR 9 NR 1	0.12	
					nasopharyngitis	36% 25%	NR NR	1.1	
	Dahl, 2006 ⁶³		SLIT (T) Placebo	61 32	throat irritation	32% 25%	NR NR	0.7	
					Stomatitis	NR NR	8 0	NA	
					Throat irritation	NR NR	151 0	NA	
					Oral paresthesia	NR NR	0 0	NA	

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Corzo, 2014 ⁷⁷ (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Stomatitis	NR NR	195 0	NA
					Throat irritation	NR NR	234 1	NA
					Oral paresthesia	NR NR	105 2	NA
Abdominal pain, nausea, vomiting/ gastrointestinal complaints	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	Nausea Treatment related	0 (0) 8 (3) 0 (0)	0 8 0	0.0
	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Abdominal pain	81 (25.2%) 17 (10.5%)	NR	0.147
					Gastrointestinal disorders	239 (74.2%) 58 (35.8%)	NR	0.384
	Pham-Thi, 2007 ⁶⁹	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 55	Gastrointestinal complaint	NR NR	19 2	NA
	Calderon, 2006 ⁶⁴	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Gastrointestinal complaints	1 0 2 1 0	NR NR NR NR NR	0.125
	Shao, 2014 ⁷⁶	Dust mite Mild asthma	SLIT (A) Pharmacotherapy	141 (54 AEs) 77 (11 AEs)	gastrointestinal intolerance	NR NR	2 (3.7%) 2 (18.18%)	NA
					Oral intolerance	NR NR	1 (1.85%) 0 (0)	NA
Local rashes	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T) Placebo	282 275 277	erosive esophagitis	0 0 1	NR	-0.004
	Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	vomiting	0	1 0	NA
	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Chelitis	36 (11.2%) 8 (4.9%)	NR NR	0.62
	Shao, 2014 ⁷⁶	Dust mite Intermittent and Mild asthma	SLIT (A) Pharmacotherapy	141 77	Local rashes	NR	5 (9.2%) 0 (0)	NA
	Mosges, 2010 ⁷⁹	Tree Pollen Mild and Moderate asthma	SLIT Placebo	27 27	Most frequent symptoms were application site itching and application site paresthesia	NR	NR	NA

T: Tablet

A: Aqueous

Table A.6 – Systemic Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Lower Respiratory	Shao, 2014 ⁷⁶	Dust mite Mild asthma	SLIT (A) Pharmacotherapy	141 (54 AEs) 77 (11 AEs)	Aggravating asthma	NR NR	8 (14.82%) 0 (0)	NA
	Pham-Thi, 2007 ⁶⁹	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 55	Asthma exacerbations	NR NR	64 67	NA
	Calderon, 2006 ⁶⁴	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Chest tightness/chest discomfort	0 0 2 (22) 0 0	NR NR 4 NR NR	0.06
					Asthma aggravated	1 (11) 0 1 (11) 0 0	1 NR 1 NR NR	0.06
					Cough	0 0 1 (11) 0 0	NR NR 1 NR NR	0.03
					Dyspnea NOS	0 1 (11) 1 (11) 0 1 (9)	NR 1 2 NR 1	-0.03
	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T)t Placebo	282 275 277	asthma [moderate, alternative etiology was “recently viral infection”]	1 0 0	NR	0.0
	Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 17	Asthma worsening or asthma exacerbations	7 total	9 total	NA
	Corzo, 2014 ⁷⁷ (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Asthma worsening or asthma exacerbations	12 total	7 6	NA
Mucosal irritation (other than mouth or	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Rhinitis	67 (20.8%) 28 (17.3%)	NR	0.035

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
GI tract)	Shao, 2014 ⁷⁶	Dust mite Intermittent and Mild asthma	SLIT aqueous Pharmacotherapy	141 77	Eye itching	NR NR	1 (1.85%) 0 (0)	NA
	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 12 SQ HDM (T) SLIT 6 SQ HDM (T) Placebo	282 275 277	Ear pruritus Treatment related	11 (4) 7 (3) 2 (1)	11 7 2	0.025
	de Blay, 2014 ⁵⁷	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM (T) SLIT 3-HQ HDM (T) SLIT 1-HQ HDM (T) Placebo	29 27 25 27	Ear pruritus	5% 3% 3% 0%	NR NR NR NR	0.0
	Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Mile and Moderate asthma	SLIT (T) Placebo	54 17	Ear pruritis	NR NR	150 0	NA
	Corzo, 2014 ⁷⁷ (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	54 18	Ear pruritis	NR NR	33 0	NA
Cutaneous	Marogna, 2013 ⁶⁵	Trees Mild asthma	BUD 400 µg/day + SLIT BUD 800 µg/day BUD 1600 BUD 400 µg/day + LTRA (Montelukast)	19 19 20 18	Generalized itching	0 0 2 0	NR NR NR NR	0.03

T: Tablet

A: Aqueous

Table A. 7 – Anaphylaxis

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	There were no anaphylactic reactions	0 0 0	0 0 0	0
Pham-Thi, 2007 ⁶⁹	Dust mite Intermittent, Mild and Moderate asthma	SLIT (T) Placebo	54 55	There were no anaphylactic reactions	0 0	0 0	0
Shao, 2014 ⁷⁶	Dust mite Intermittent and Mild asthma	SLIT (A) Pharmacotherapy	141 77	There were no anaphylactic reactions	0 0	0 0	0
Mosges, 2010 ⁷⁹	Tree Pollen Mild and Moderate asthma	SLIT (A) (ultra-rush) Placebo	27 27	There were no anaphylactic reactions	0 0	0 0	0
Maloney, 2016 ⁶⁰	Grass, Cat, Dog, Mold, Birch,	SLIT - 6 SQ-HDM (T) SLIT - 12 SQ-HDM (T)	22 24	There were no anaphylactic reactions	0 0	0 0	0

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Mugwort Severity NS	Placebo	33		0	0	

T: Tablet A: Aqueous

Table A.10 – Deaths*

Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 6 SQ HDM (T) SLIT 12 SQ HDM (T) Placebo	275 282 277	There were no deaths reported	0	0
Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT (T) Placebo	322 162	There were no deaths reported	0	0
Bufe, 2009 ⁷⁸	Timothy Grass Mild, Moderate ad Severe asthma	SLIT (T) Placebo	126 127	There were no deaths reported	0	0

T: Tablet A: Aqueous

*Data abstracted ONLY if studies specifically reported on deaths

Table A.11 – Other reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
No reactions reported	La Grutta, 2007 ⁷¹	Dust mite Severity NS	SLIT Concomitant pharmacotherapy	33 23	No local or systemic relevant adverse events were observed	NR NR	0 0	NA
	Mosges, 2010 ⁷⁹	Tree Pollen Mild and Moderate asthma	SLIT aqueous (ultra-rush) Placebo	27 27	No serious systemic effects were observed	0 0	NR	NA
	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	AEs or Adverse Drug Reactions life-threatening or disabling	0 0	0 0	0
	Corzo, 2014 ⁷⁷ (adults) Trial 1	Dust mite Mild and Moderate asthma	SLIT tablet Placebo	54 17	There were no serious adverse events	0 0	0 0	0
	Corzo, 2014 ⁷⁷ (peds) Trial 2	Dust mite Mild and Moderate asthma	SLIT tablet Placebo	54 18	There were no serious adverse events	0 0	0 0	0

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)
	Pham-Thi, 2007 ⁶⁹	Dust mite Intermittent, Mild and Moderate asthma	SLIT tablet Placebo	54 55	There were no multiple-organ life-threatening events	0 0	0 0	0
Reactions not specified	Calderon, 2006 ⁶⁴	Grass Mild and Moderate asthma	SLIT 75000 SQ-T SLIT 150000 SQ-T SLIT 300000 SQ-T SLIT 500000 SQ-T Placebo	9 9 9 5 11	Not specified	0 0 0 0 1 (9%)	NR NR NR NR NR	-0.091
	Pham-Thi, 2007 ⁶⁹	Dust mite Intermittent, Mild and Moderate asthma	SLIT T Placebo	54 55	total number of adverse events, local and systemic	0 4 (10%)	NR	-0.073
	Bufe, 2009 ⁷⁸	Timothy Grass Mild, Moderate and Severe asthma	SLIT (T) Placebo	126 127	the pattern of adverse events was similar for subjects with and without asthma symptoms.	109 (87%) 106 (83%)	426 278	0.030
	Maloney, 2016 ⁶⁰	Grass, Cat, Dog, Mold, Birch, Mugwort Severity NS	SLIT - 6 SQ-HDM T SLIT - 12 SQ-HDM T Placebo	22 24 33	Adverse events not specified (TEAEs)	68% 50% 46%	NR	0.013
					Adverse events not specified (TRAEs)	55% 50% 32%	NR	0.009
	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Severe Adverse Drug Reaction SLIT vs placebo P NS	10 (3.1%) 3 (1.9%)	NR	0.013
					Moderate Adverse Drug Reaction SLIT vs placebo P =0.0003	96 (29.8%) 24 (14.8%)	NR	0.150
					Mild Adverse Drug Reaction SLIT vs placebo P<0.0001	228 (70.8%) 70 (43.3%)	NR	0.276
					Severe AE SLIT vs placebo P NS	17 (5.3%) 10 (6.2%)	NR	-0.009
					Moderate AEs SLIT vs placebo P NS	149 (46.3%) 63 (38.9%)	NR	0.074
					Mild AEs SLIT vs placebo P NS	259 (80.4%) 101 (62.3%)	NR	0.181
					Serious AE	7 (2%) 10 (4%) 11 (4%)	10 (1%) 10 (1%) 12 (2%)	-0.40
	Virchow, 2016 ⁵⁶	Dust mite Severity NS	SLIT 12 SQ HDM T SLIT 6 SQ HDM T Placebo	282 275 277	AEs leading to discontinuation	25 (9%) 12 (4%) 8 (3%)	46 (6%) 23 (3%) 10 (2%)	-0.29
	de Blay, 2014 ⁵⁷	Dust mite Mild and Moderate	SLIT 6-HQ HDM T SLIT 3-HQ HDM T	134 131	Serious adverse events	6 3	7 3	-0.37

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)	Calculated risk difference (for AEs reported as patients)			
		asthma	SLIT 1-HQ HDM T Placebo	117 107		6 4	7 5				
Infection	Devillier, 2016 ⁶¹	Dust mite Mild and Moderate asthma	SLIT Placebo	322 162	Infections and infestations	67 (20.8%) 10 (18.5%)	NR	0.146			
		Dust mite Mild asthma	SLIT (A) Pharmacotherapy	141 (54 AEs) 77 (11 AEs)	Upper respiratory tract infection	NR	23 (42.5%) 7 (63.6%)	NA			
Unable to categorize	Shao, 2014 ⁷⁶				Nosebleed	NR	1 (1.85%) 1 (9.09%)	NA			
					Headache	NR	0 (0) 1 (9.09%)	NA			
	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	134 131 117 107	dizziness	0 1 0 0	NR NR NR NR	0				
				migraine	0 0 1 0	NR NR NR NR	0				
	de Blay, 2014 ⁵⁷	Dust mite Mild and Moderate asthma	SLIT 6-HQ HDM SLIT 3-HQ HDM SLIT 1-HQ HDM Placebo	134 131 117 107	Accidental overdose Treatment related	4 (1) 15 (5) 9 (3)	5 16 12	-0.032			
					Arthralgia	0 1 0	NR	0			
					hepatocellular injury	0 0 1	NR	-0.004			
	Virchow, 2016 ⁵⁶	Dust mite NS	SLIT 6 SQ HDM tablet SLIT 12 SQ HDM tablet Placebo	275 282 277							

T: Tablet

A: Aqueous

TRAE: Treatment related adverse event

TEAE: Treatment emergent adverse event

SECTION B SLIT Safety for NON RCTs

Table B.1 – Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
Adults	Dunsky, 2006 ⁸⁰ US	SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT NS	Polysensitized perennial and seasonal tree nut and peanut allergy	Multiple allergens	Home
	Vovolis, 2013 ⁸¹	SLIT (A) wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE Not reported	Polysensitized Olea europaea pollen, Dust mite (Dpter-D far)	Multiple allergens	Clinic

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting
	Ventura, 2008 ⁸² Europe	SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Not reported	Polysensitized graminacee, olive, cypress, house dust mite, Anisakis	Single allergen Dust mite (Dpter-D far)	NR
	Blazowski, 2008 ⁸³	SLIT wo comparator	Asthma diagnosis criteria NR Severity NS Control status NS	Not reported	Not reported	Multiple allergens	Home
Mixed age	Roger, 2011 ⁸⁴ Europe	SLIT wo comparator	Asthma diagnosis criteria NR Severity Mild persistent and moderate persistent Control status NS	SPT and IgE Positive SPT (size NS) plus specific IgE class 2 or greater (10.7 kU/l)	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic
	De Castro, 2013 ⁸⁵	SLIT (T) Control	Asthma diagnosis criteria NR Mild persistent and moderate persistent Controlled	SPT and IgE Wheel diameter > 3mm; or IgE CAP class 3	Both poly and monosensitized	Single allergen Grass	Not specified
Children	Nuhoglu, 2007 ⁸⁶	SLIT wo comparator	Asthma diagnosis criteria NR Severity Intermittent Controlled	SPT >3mm	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Home and Clinic
	Galip, 2015 ⁸⁷ Europe	SLIT (A) wo comparator	Pulmonary tests (PFT with bronchodilator reversibility of 18%) persistent asthma controlled on daily ICS	SPT wheal 10x10mm	Monosensitized Dust mite (Dpter-D far))	Single allergen Dust mite (Dpter-D far)	Home Hospital after AE

T: Tablet A: Aqueous SPT: Skin prick test

IgE:ImmunoglobulinE

NS: Not specified

Dpter: *Dermatophagoides pteronyssinus*Dfar: *Dermatophagoides farina*

* Authors did not report sensitization status

Table B.2 – Patient Characteristics

Population	Study	Patients	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/ Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean years Affected)
Adults	Dunsky, 2006 ⁸⁰ US	1	SLIT wo comparator	31 years	NR/1	1/NA	NR
	Vovolis, 2013 ⁸¹	1	SLIT wo comparator	25 years	NR/1	1/NA	15 years
	Ventura, 2008 ⁸² Europe	1	SLIT wo comparator	39 years	NR/1	1/NA	NR
	Blazowski, 2008 ⁸³	1	SLIT wo comparator	16 years	NR/1	1/NA	NR
Mixed age	Roger, 2011 ⁸⁴ Europe	NR	SLIT wo comparator	20.4 (NR)	46.3%/53.7%	77/NA	4.84 years
	De Castro, 2013 ⁸⁵ Europe	98	SLIT Control	NR NR	NR NR	NR NR	NR
Children	Nuhoglu, 2007 ⁸⁶	39	SLIT wo comparator	8.8 (2.3)	23/16	39/NA	NR

Population	Study	Patients	Comparators	Age in years Mean +/- SD (range)	Sex (% Male/ Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean years Affected)
	Galip, 2015 ⁸⁷	1	SLIT wo comparator	6 years	1/NR	1/NA	3 years

Table B.3 – Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Dunsky, 2006 ⁸⁰	SLIT without comparator	NR	NR	NR	NR	NR	NR
	Vovolis, 2013 ⁸¹	SLIT without comparator	NR	Targeted: NR Actual: 3 drops /day	NR	Daily	NR	NR
	Ventura, 2008 ⁸²	SLIT without comparator	NR	NR	NR	NR	NR	1 month
	Blazowski, 2008 ⁸³	SLIT without comparator	NR	Targeted: 10 drops, 100 IR/ml Actual: 60 drops, 100 IR/ml	NR	Daily	NR	3 years
Mixed age	Roger, 2011 ⁸⁴	SLIT without comparator	NR	Targeted: 240 IR 3 times per week Actual: NR	Targeted: 450 IR at the end of ultra-rush induction Actual: NR	3 times per week	NR	2 weeks
	De Castro, 2013 ⁸⁵	SLIT Control	Both (SABAs ICS and oral corticosteroids)	Targeted: 2-5 weekly tablets of 1.000 UA each Actual: 2-5 weekly tablets of 1.000 UA each Targeted: NA Actual: NA	NR	Daily	NR	3 years
Children	Nuhoglu, 2007 ⁸⁶	SLIT without comparator	NR	Targeted: NR Actual: NR	Targeted: NR Actual: 100	3 alternate days a week	NR	3 years
	Galip, 2015 ⁸⁷	SLIT without comparator	Both	Targeted: 300 IR/ml Actual: 300 IR/ml	NR	Daily	NR	3 years

NR: Not reported

IR: index reactivity units

Table B. 4 – Hypersensitivity

No studies reported specifically on hypersensitivity reactions, however all local, systemic, anaphylactic, and some of the “other” reactions should be noted to fall under the umbrella of hypersensitivity reactions.

Table B.5 – Local Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
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Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Abdominal pain, nausea, vomiting/ Gastrointestinal complaints	Ventura, 2008 ⁸²	Dust mite NS	SLIT aqueous wo comparator	1	abdominal pain, nausea, vomiting	1	NR

Table B.6 – Systemic Reactions

Category	Study	Allergen and Asthma Severity	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Lower respiratory	Galip, 2015 ⁸⁷	Dust mite NS	SLIT aqueous wo comparator	2	Wheezing requiring beta agonists and dose reduction of SLIT	1	NA
	Nuhoglu, 2007 ⁸⁶	Dust mite Mild and Moderate asthma	SLIT tablet wo comparator	39	Asthma attacks	NR	0.44
	De Castro, 2013 ⁸⁵	Grass and Dust mite Mild and Moderate asthma	SLIT Control	50 48	Worsening of asthma	2% 0	1 0
Reactions not specified	De Castro, 2013 ⁸⁵	Grass and Dust mite Mild and Moderate asthma	SLIT Control	50 48	No systemic adverse effects were reported during the 3 years	0 0	0 0
	Roger, 2011 ⁸⁴	Dust mite Intermittent, Mild and Moderate asthma	SLIT aqueous rush wo comparator	77	Adverse events not specified A little under half the adverse events were reported in the 77 asthmatic patients included in the study, although the profile of adverse events was similar to the overall population of the study.	NR	NR

Table B.7 - Anaphylaxis

Study	Allergen and Asthma severity	Arms	N	Description	Reported as patients N (%)	Reported as events N (%)
Blazowski, 2008 ⁸³	Dust mite Intermittent asthma	SLIT aqueous	1	Anaphylactic shock	1	NR
Vovolis, 2013 ⁸¹	Dust mite and Trees NS	SLIT aqueous	1	Flushing, hoarseness, dyspnea, dizziness and mild hypotension	1	NR
Dunsky, 2006 ⁸⁰	Mold, Animals, Grass, and Weeds NS	SLIT aqueous	1	Anaphylaxis	1	NR

Table B.8 – Deaths*

No study reported on deaths.

*Data abstracted ONLY if studies specifically reported on deaths

Appendix H: Sublingual versus subcutaneous immunotherapy

Sublingual versus Subcutaneous Immunotherapy

TABLE 1. Study Characteristics

Population	Author Country	Comparators	Asthma Diagnosis	Allergy Diagnosis	Number and Type of Allergen to which Patients were Sensitized	Allergen Provided in AIT	Setting	Study Design Population
Adults	Mungan, 1999 ⁸⁸ Turkey	SCIT VS. SLIT	Asthma diagnosis per clinical criteria and pulmonary tests (reversibility and FEV >70%) Severity NS Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic	RCT Adults >18
Mixed age	Li, 2016 ⁸⁹ Asia	SCIT VS. SLIT	Asthma diagnosis per Chinese medical association Pulmonary tests (bronchial provocation test or exercise test positivity) Severity NS Control status presence of symptoms despite optimal treatment and allergen avoidance uncontrolled asthma excluded	SPT and IgE wheal ≥ 0.25 , IgE >0.35 kU/L	Mono vs Polysensitized unclear* All patients sensitized to Dust mite (Unspecified dust mites)	Single allergen Dust mite (NS)	Clinic	RCT Children and adults 5-14
	Yukselen, 2012 ⁹⁰ Yukselen, 2013 ^{91*} Turkey	SCIT VS. SLIT	Asthma diagnosis per GINA criteria Mild persistent Control status NS	SPT and IgE SPT >3 mm IgE class II or >0.70 kU/l	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic	RCT Children and adults 6-14
Children	Keles, 2011 ⁹² Turkey	SCIT VS. SLIT	Asthma diagnosis per GINA criteria and pulmonary tests (reversibility and FEV >70%) Mild persistent and moderate Control status NS	SPT and IgE NS	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic	RCT Children 5-12yo
	Karakoc-Aydiner, 2015 ⁹³ Eifan, 2010 ⁹⁴ Europe	SCIT VS. SLIT	Asthma diagnosis per EPR and GINA criteria Mild persistent and moderate persistent Controlled asthma	SPT and IgE IgE >0.35 positive SPT (size not described)	Monosensitized Dust mite (Dpter-D far)	Single allergen Dust mite (Dpter-D far)	Clinic	RCT Children 5-11yo
	Cochard, 2009 ⁹⁵ Europe	SCIT vs SLIT	Asthma diagnosis criteria NR Severity NS Control status NS	SPT and IgE NS	Polysensitized Patient 1: birch, hazel tree, grass mix, rye, plantain, ragweed pollens, Alternaria; Patient 2: grass and cereal pollens, dust mites, molds, cat dander	Multiple allergens	Clinic for SCIT NR for SLIT	Case report Children 14 and 18

* Authors do not specify sensitization status

** This is a second phase, Yukselen, 2013⁹¹, not included because is an open phase Cohort

TABLE 2. Study Characteristics

Population	Study	Patients Randomized	Comparators	Age in Years Mean +/- SD (range)	Sex (% Male/Female)	Patients Enrolled/ Dropouts	Duration of Disease (Mean Years Affected)
Adults	Mungan, 1999 ⁸⁸	36	SLIT SCIT Placebo	32+/- 7 (Range 18-41) 29 +/- 7 (Range 18-39) 33 +/- 8 (Range 18-46)	13/87 40/60 9/91	15/0 10/0 11/0	5.67+/-4.32 years 6.2 +/-2.97 years 7.27 +/-3.07 years
Mixed age	Li, 2016 ⁸⁹	90	SCIT + Seretide SLIT aqueous + Seretide Seretide	7.6 +/- 1.5 7.4 +/- 1.3 7.1 +/- 1.2	63/37 60/40 63/37	27/3 30/0 30/0	1.7 1.6 1.6
	Yukselen, 2012 ⁹⁰	32	SCIT + placebo drops SLIT + placebo injections Placebo injections + drops	11+/- 3 9+/- 3 10+/- 3	60/40 50/50 60/40	10/0 11/1 10/1	1 year
Children	Keles, 2011 ⁹²	60	SCIT SLIT SCIT + SLIT Pharmacotherapy	7+/- 2 9+/- 2 8+/- 1 8+/- 3	36/74 31/69 56/44 42/58	11/2 13/2 14/0 12/0	NR
	Karakoc-Aydiner, 2015 ⁹³ Eifan, 2010 ⁹⁴	48	SLIT SCIT Pharmacotherapy	6 +/- 2 (Range 5-10) 7 +/- 2 (Range 5-10) 7 +/- 2 (Range 5-10)	47/53 38/62 44/56	16/1 16/2 16/2	2.1 years 2.5 years 2.4 years

TABLE 3. Intervention Characteristics

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
Adults	Mungan, 1999 ⁸⁸	SLIT SCIT Placebo SLIT	conventional therapy	20 drops of 100 IR/ml 0.15-0.75 ml of 10 IR/ml	11316 IR 131 IR	2 times a week Monthly	NR NR	1 year
Mixed age	Li, 2016 ⁸⁹	SCIT + Seretide SLIT aqueous + Seretide Seretide	Both	SCIT conventional 0.1-0.8 mL of 100000 SQ-U/MI SLIT 3 drops of 333 µg/mL daily	NR	SCIT Weekly SLIT daily	NR	16 weeks
	Yukselen, 2012 ⁹⁰	SCIT (plus placebo sublingual drops) SLIT (plus placebo subcutaneous injections) Placebo (sublingual and subcutaneous)	conventional therapy	0.2-0.8 ml of 5000 TU/ml 28 drops of 1000 TU/ml	43,770 TU (21,885 TU of Dpt and 21885 TU of Df) 173733 TU (86866.5 TU of Dpt and 86,866.5 TU of Df)	Every 4 th week Three times a week	NR NR	1 year

Population	Study	Arms	Control/ Rescue Therapy	Maintenance Dose	Cumulative Dose	Maintenance Dosing Interval	Quantity of Major Protein (µg)	Treatment Duration
	Eifan, 2010 ⁹⁴	SLIT SCIT Pharmacotherapy	Only rescue medication	5 drops STU (1000 STU/ml) 100000 SQ U/ml, 1cm ³	73876.8 STU 1131540 SQU	3 times per week Monthly	295.5 Der p 1, 295.5 Der f 1(cumulative) 111 Der p 1, 156 Der f 1(cumulative)	1 year
Children	Keles, 2011 ⁹²	SCIT SLIT SCIT (build-up) +SLIT (maintenance) Pharmacotherapy	Only rescue medication	44.12 µg of Der p1 and 62.1 µg of Df1 52.8 µg of Der p1 and 52.8 µg of Df1 43.2 µg of Der p1 and 43.2 µg of Df1	NR	Monthly 3 times a week 3 times a week	44.12 µg of Der p1 and 62.1 µg of Df1 52.8 µg of Der p1 and 52.8 µg of Df1 43.2 µg of Der p1 and 43.2 µg of Df1 (Maintenance phase)	1 year

TABLE 4. Asthma Control

Asthma symptoms ACT Scores

Study	Allergen	Arms	N	Time of Measure	Value pre Mean+/-SD	Value post	Comparative Values
Li, 2016 ⁸⁹ Asia	Unspecified Dust mites	SCIT + Seretide SLIT aqueous + Seretide Seretide	27 30 30	NR	18.84 (3.11) 19.06 (3.51) 18.74 (3.33)	24.75 (1.82) 23.35 (2.13) 23.01 (2.66)	SCIT pre vs post $P < 0.05$ SLIT pre vs post $P < 0.05$ Seretide pre vs post $P < 0.05$

TABLE 5. Quality of Life

No study reported on quality of life.

TABLE 6. Medication Use

No study reported on medication use

TABLE 7. Asthma Exacerbations and Healthcare Utilization

No study reported on Asthma exacerbations or healthcare utilization.

TABLE 8. Pulmonary Physiology and Airway Responsiveness

Study	Allergen	Arms	Time of Measure	Outcome Description	Value pre	Value post	Comparative Values
Li, 2016 ⁸⁹	Unspecified Dust mites	SCIT + Seretide SLIT (A) + Seretide Seretide	16 weeks	Peak expiratory flow (PEF)	81.79 +/- 8.60 80.65 +/- 8.60 79.69 +/- 8.02	89.56 +/- 4.21 88.77 +/- 6.42 89.95 +/- 5.59	SCIT pre vs post $P < 0.01$ SLIT pre vs post $P < 0.05$ Seretide pre vs post P NR
Li, 2016 ⁸⁹	Unspecified Dust mites	SCIT + Seretide SLIT (A) + Seretide Seretide	16 weeks	FEV1	77.25 +/- 6.6 77.65 +/- 5.71 75.66 +/- 4.06	89.79 +/- 9.55 87.35 +/- 9.96 79.63 +/- 7.05	SCIT pre vs post $P < 0.05$ SLIT pre vs post $P < 0.05$ Seretide pre vs post P NR
Mungan, 1999 ⁸⁸	Dust mites	SLIT SCIT Placebo	1 year	Methacholine bronchial provocation test	NR	NR	SLIT pre vs post $P=NS$ SCIT pre vs post $P=NS$ Placebo pre vs post $P=NS$
Yukseken, 2012 ⁹⁰	Dust mites	SCIT SLIT Placebo	1 year	HDM-Specific Bronchial provocation	NR	NR	SCIT pre vs post, $P=0.03$ SLIT pre vs post, $P=0.56$ Placebo pre vs post, $P=0.78$ SCIT vs SLIT $P=0.91$

PFT: Pulmonary Function Test

NS: Not significant

PEF: Peak Expiratory Flow

FEV: forced expiratory volume

TABLE 9. Immunological Markers**A. IgE**

Study	Allergen	Arms	Time of Measure	Outcome/Unit	Value pre	Value post	Comparative Values
Eifan, 2010 ⁹⁴	Dust mite	SLIT SCIT Pharmacotherapy	1 year	IgE D.f/ D.pt specific IU/ml	51.1±38.9/ 59.4 ±42.9 63.6±37.7/ 69.8±45.3 60.4±37.7/ 72.4±29.5	NR NR NR	D.f specific: SCIT pre versus post $P=0.03$ SCIT versus Pharmacotherapy $P=0.03$ SLIT pre versus post $P=0.04$ Pharmacotherapy pre versus post $P=NS$ D.pt specific: SCIT versus Pharmacotherapy $P=0.03$
Mungan, 1999 ⁸⁸	Dust mite	SLIT SCIT Placebo	1 year	IgE D.f/ D.pt specific kU/ml	505.05 311.89 288.40	NR NR NR	No significant changes in all three arms at 12 months compared to baseline
Keles, 2011 ⁹²	Dust mites	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgE IU/ml	62+/-52 67+/-33 83+/-27 73+/-37	61+/- 53 44+/-32 85+/-34 75+/-41	No significant differences pre vs post in all groups. No significant differences between IT groups and pharmacotherapy
2006 Li, 2016 ⁸⁹	Unspecified dust mite	SCIT + Seretide SLIT aqueous + Seretide Seretide	NR	HDM specific IgE	17.02+/- 9.25 18.62 +/-8.32) 17.89 +/-8.78)	11.12 +/- 8.27 13.07 +/- 9.15 16.07 +/- 9.35	$P < 0.01$ $P < 0.05$ NR

B. IgG4

Study	Allergen	Arms	Time of Measure	Biomarker	Units	Value pre	Value post	Comparative Values
Keles, 2011 ⁹²	Dust mites (D.pt and D.f)	SCIT SLIT SCIT+SLIT Pharmacotherapy	1 year	Derp1 specific IgG4	Ua/ML	0.21+/0.37 0.14+/0.1 0.11+/0.03 0.11+/-0.11	0.22+/-0.41 5.74+/-4.43 0.70+/-0.45 0.09+/-0.08	SCIT vs Pharmacotherapy p<0.05 SCIT+SLIT vs Pharmacotherapy p<0.05

TABLE 10. Anaphylaxis

Study	Arms	N	Event description	Reported as patients N (%)	Reported as Events N (%)
Eifan, 2010 ⁹⁴	SLIT SCIT	16	Flushing, wheezing and dyspnea requiring adrenaline - required treatment discontinuation (SCIT arm)	1 (0.06%)	-

TABLE 11. Hypersensitivity

No study reported on hypersensitivity.

TABLE 12. Local Reactions

Study	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N(%)
Mungan, 1999 ⁸⁸	SLIT SCIT Placebo	15 10 11	Reaction at the injection site classified > 5cm (SCIT)	2 (13%)	-
			Buccal pruritus (SLIT)	1 (10%)	-
Eifan, 2010 ⁹⁴	SLIT SCIT Pharmacotherapy	16	Oral cavity or Oropharynx Itching classified as mild (SLIT)	1 (0.06%)	-
Li, 2016 ⁸⁹	SCIT + Seretide SLIT aqueous + Seretide Seretide	27 30 30	Local AEs grade 1	10 3 NR	NR NR NR
			Local AEs grade 2	1 1 NR	NR NR NR

TABLE 13. Systemic Reactions

Study	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
Eifan, 2010 ⁹⁴	SLIT SCIT	16	Respiratory reaction- severe asthma symptoms-classified as severe – required treatment discontinuation (SCIT arm)	1 (6.2%)	-
Mungan, 1999 ⁸⁸	SLIT SCIT	15 10	Respiratory events classified as mild (bronchospasm) in SCIT	1 (10%)	-

Study	Arms	N	Event Description	Reported as Patients N (%)	Reported as Events N (%)
	Placebo	11	Mild Nausea in SLIT	1 (10%)	-
Keles, 2011 ⁹²	SCIT SLIT SCIT+SLIT Pharmacotherapy	11	Respiratory events classified as moderate- dyspnea and wheezing- required treatment discontinuation (SCIT arm)	2 (18.2%)	-
Li, 2016 ⁸⁹	SCIT + Seretide SLIT aqueous + Seretide Seretide	27 30 30	Unspecified systemic reactions	2 (SCIT) 1 (SLIT)	

Reactions Reported in Non RCTs

Study	Allergen and Asthma severity	N	Arms	Event Description
Cochard, 2009 ⁹⁵	Case 1 Multiple Asthma severity NS	1	SCIT	Recurrent immediate itchy and painful large local reactions at the injection site lasting for 2 to 4 days, in the absence of any systemic side effects – Required treatment discontinuation and switched to SLIT
			SLIT	SLIT ultrarush- Mouth itchiness during build up asthma attacks, during treatment progression- required discontinuation
	Case 2 Multiple Asthma severity NS	1	SCIT	shortness of breath and was wheezing required treatment with antihistamine. AE recurred with second dose– Required treatment discontinuation and switched to SLIT
			SLIT	SLIT ultrarush- heavy nasal congestion during build up only with dust mite preparation. Reoccurred when initiated followed with increased symptoms of asthma during treatment progression- required discontinuation

TABLE 14. Deaths

No deaths reported.

Appendix I. Risk of Bias

Appendix I. Risk of Bias

Subcutaneous Immunotherapy (SCIT)

Table 1 – Cochrane Risk of Bias for RCTs Included for SCIT

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Participants of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Alzakar, 2010 ³⁴	Unclear	Unclear	No	No	No	Yes	Yes	Medium
Altintas, 1999 ¹⁹	Unclear	No	No	No	No	Yes	Yes	High
Ameal, 2005 ⁴	Unclear	Yes	Yes	Yes	No	Yes	Yes	Low
Adkinson, 1997 ³² Limb, 2006 ³³	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Arroabarren, 2015 ³¹	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Baris, 2014 ²⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Blumberga, 2011 ¹³	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Bousquet, 1985 ³	Unclear	Low	No	No	No	Low	No	High
Bousquet, 1988 ²³	Yes	No	No	No	No	Yes	Yes	High
Casanovas, 2005 ³⁷	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Medium
Chakraborty, 2006 ⁸	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Creticos, 1996 ⁹	Yes	No	No	No	Yes	Yes	No	High
Dreborg, 1986 ²⁹	Yes	Yes	No	Unclear	Yes	Yes	Yes	Low
Gallego, 2010 ² Garcia-Robaina, 2006 ¹	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Garcia-Ortega, 1993 ¹²	Yes	No	No	No	Yes	Yes	No	High
Hill, 1982 ²⁰	Unclear	No	No	No	No	Yes	Yes	High
Hui, 2014 ³⁰	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Low

Study	Sequence generation	Allocation scheme concealed	Blinding of participants and personnel	Blinding of participants of outcomes assessor	Incomplete outcome data addressed	Selective reporting	Other biases (other threats to validity)	Overall Risk of Bias
Ibero, 2006 ¹⁷	Unclear	Unclear	No	No	Yes	Yes	Yes	Medium
Kilic, 2011 ²⁵	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Kohno, 1998 ⁷	Unclear	No	No	Unclear	Yes	Yes	Yes	Medium
Lozano, 2014 ²⁶	No	No	No	No	Yes	Yes	Yes	High
Maestrelli, 2004 ¹⁶	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Low
Ohman, 1984 ¹⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Olsen, 1997 ⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pifferi, 2002 ²⁸	Yes	No	No	Unclear	Yes	Yes	Yes	Medium
Roberts, 2006 ³⁹	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Schubert 2009 ³⁸	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Tsai, 2010 ³⁵	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Van Bever, 1992 ¹⁸	Unclear	Yes	No	Unclear	Yes	Yes	No	Medium
Van Metre, 1988 ¹¹	Unclear	No	Yes	Yes	No	Yes	No	High
Valovirta, 1984 ²¹ Valovirta, 2006 ²²	Yes	Yes	Yes	Unclear	Low	Yes	Yes	Low
Vidal, 2011 ⁵	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Wang, 2006 ¹⁵	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zielen, 2010 ²⁷	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium

(in alphabetical order)

Table 2 – ROBINS I Risk of Bias for non-RCTs Included for SCIT

Study	Bias due to Confounding	Bias in Selection of Participants	Bias of Classification of Interventions	Bias due to Departure from intended interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall ROB
Confino-Cohen, 2010 ⁵⁰	High	Moderate	Low	Low	Low	Serious	Moderate	Serious
Eng, 2006 ⁵⁵	Probably Not	Moderate	Low	Low	Moderate	Low	Low	Moderate
Gozde Kanmaz, 2011 ⁴⁸	High	Critical	Serious	Low	Low	Low	Low	Serious
Quiralte, 2013 ⁴⁰	High	Moderate	Low	Low	Low	Moderate	Low	Moderate
Rank, 2008 ⁴¹	Yes	Serious	Serious	Moderate	No information	Low	Moderate	Serious
Santos, 2015 ⁵⁴	High	Moderate	Low	Low	Unclear	Moderate	Low	Moderate
Smits, 2007 ⁵¹	Probably Not	Moderate	Low	Low	Low	Low	Low	Low

Table 3 – WHO assessment for Case Series and Case Reports Included for SCIT

Study	How was the Adverse Event Classified?	Was the Adverse Event Related to the Intervention?	Causality
Kartal, 2015 ⁴⁵	Not clear	Yes	Unassessible/Unclassifiable
Santos, 2015 ⁵⁴	Dose related and time related	Not reported	Probably/likely
Rank, 2014 ⁴²	Dose related	Yes	Certain
Sana, 2013 ⁴³	Not dose related	Yes*	Unlikely
Cardona, 2014 ⁵³	Dose related and time related	Yes	Probably/likely
Copenhaver, 2011 ⁴⁹	Dose related and time related	Yes	Probably/likely
Kim, 2011 ⁴⁴	Dose related and time related	Yes	Certain
Ozden, 2009 ⁴⁷	time related	Yes	Probable/likely
Sanchez-Morillas, 2005 ⁴⁶	time related	Yes	Possible
Garde, 2005 ⁹⁷	Dose related	Not reported	Unassessible/Unclassifiable

*As reported by authors

Sublingual Immunotherapy (SLIT)

Table 4 – Cochrane Risk of Bias for RCTs Included for SLIT

Study	Sequence Generation	Allocation Scheme Concealed	Blinding of Participants and Personnel	Blinding of Participants of Outcomes Assessor	Incomplete Outcome Data Addressed	Selective Reporting	Other Biases (other threats to validity)	Overall Risk of Bias
Bahceciler, 2001 ⁷⁰	Yes	Yes	No	No	Yes	Yes	No	Medium
Bufe, 2009 ⁷⁸	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Medium
de Blay, 2014 ⁵⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Calderon, 2006 ⁶⁴	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Dahl, 2006 ⁶³	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Medium
Devillier, 2016 ⁶¹	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Medium
Ippoliti, 2003 ⁷⁴	Yes	No	Yes	Unclear	Yes	No	Yes	Medium
La Grutta, 2007 ⁷¹	Unclear	No	No	No	No	No	Yes	High
Lue, 2006 ⁷²	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Medium
Maloney, 2016 ⁶⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Marogna, 2009 ⁶⁷	Yes	Yes	No	No	Yes	Yes	No	Medium
Marogna, 2010 ⁶⁸	Yes	No	No	No	Yes	Yes	No	High
Marogna, 2013 ⁶⁵	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Mosges, 2010 ⁷⁹	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	High
Niu, 2006 ⁷³	Yes	Yes	Yes	Unclear	No	No	Yes	Medium
Pham-Thi, 2007 ⁶⁹	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low
Virchow, 2016 ⁵⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Voltolini, 2010 ⁶⁶	Yes	Yes	No	Unclear	Yes	Yes	No	Medium

(in alphabetical order)

Table 5 – ROBINS I Risk of Bias for non-RCTs Included for SLIT

Study	Bias due to Confounding	Bias in Selection of Participants	Bias of Classification of Interventions	Bias due to Departure from intended interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall ROB
De Castro, 2013 ⁸⁵	Low	Low	Low	Low	Low	Moderate	Moderate	Low
Nuhoglu, 2007 ⁸⁶	High	Moderate	Low	Low	Unclear	Low	Low	Moderate
Roger, 2011 ⁸⁴	Probably Not	Moderate	Low	Low	Low	Moderate	Low	Low

Table 6 – WHO assessment for Case Series and Case Reports Included for SLIT

Study	How was the Adverse Event Classified?	Was the Adverse Event Related to the Intervention?	Causality
Galip, 2015 ⁸⁷	Dose related	Yes	Certain
Vovolis, 2013 ⁸¹	Dose related	Yes	Probable/likely
Ventura, 2008 ⁸²	Ends with withdrawal	Yes	Probable/likely
Blazowski, 2008 ⁸³	Dose related	Yes	Certain
Dunsky, 2006 ⁸⁰	Dose related and time related	Yes	Certain

Table 7 – Cochrane Risk of Bias for RCTs for SCT vs. SLIT

Study	Sequence generation	Allocation scheme concealed	Blinding of participants and personnel	Blinding of outcomes	Incomplete outcome data	Selective reporting	Free of other biases (other threats to validity)	Overall Risk of Bias
Li, 2016 ⁸⁹	Unclear	Unclear	No	No	Yes	Yes	Yes	Medium
Karakoc-Aydiner, 2015 ⁹³ Eifan, 2010 ⁹⁴	Unclear	Yes	No	No	Yes	Yes	Yes	Low
Mungan, 1999 ⁸⁸	Unclear	No	No	No	Yes	Yes	Yes	Medium
Keles 2011 ⁹²	Yes	No	No	No	Yes	Yes	Yes	Medium
Yukselen, 2012 ⁹⁰	Yes	Yes	Yes	No	Yes	Yes	Yes	Medium

Appendix J. References

Appendix J. References

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